acta

physiologica

latino

americana

VOLUMEN IX
Nº 3

1959

ACTA PHYSIOLOGICA LATINOAMERICANA

Editada por la Asociación Ciencia e Investigación

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BRASIL: Editora Guanabara, Weissmann-Koogan, Ltda.
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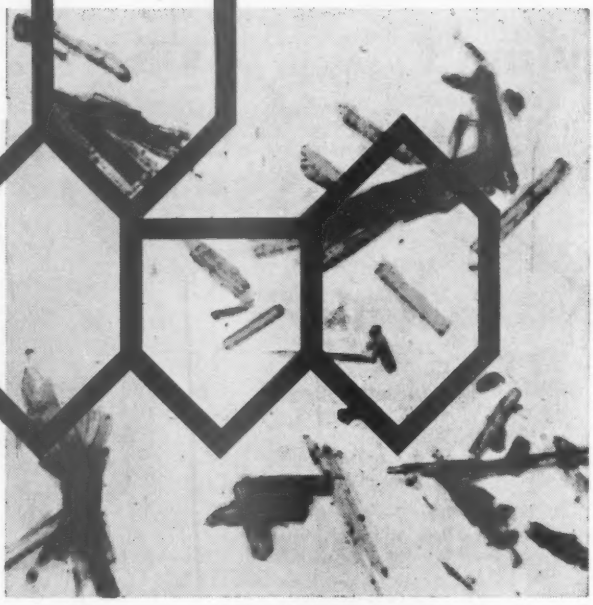

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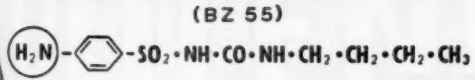

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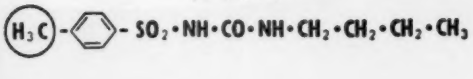

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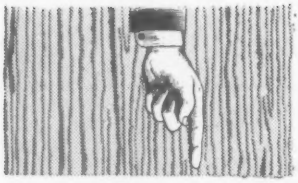

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CIRCULATORY AND RESPIRATORY ADJUSTMENTS TO HYPOXIA AND TO LIGHT EXERCISE IN NORMAL YOUNG MEN (*)

J. García Ramos (**) and R. Reynaud A. (***)

(Escuela Médico Militar, A. C., México.)

There are numerous papers published on the circulatory and respiratory changes which occur during conditions of hypoxia or during physical exercise. In the present study, it was tried to find a basis for the hypothesis presented in a previous paper by one of us (4) that circulatory adaptations to respiratory function in conditions of exaggerated demands are very similar during hypoxia and during physical exercise. For this reason, the present observations were planned to cover just a particular case of hypoxia by rebreathing (carbon dioxide being removed by absorption) as well as one of exercise, the standard step test. Another aspect of this study is its contribution to physiological data from people living at a place above sea level, as the observations were made at the altitude of Mexico City (2268 meters above sea level) on young men more or less acclimatized to it.

Method

The observations were made on a group of 50 young men, from 17 to 22 years of age, students forming the first grade of this medical school. All of them living under similar conditions of food intake, physical work and habits, as they live as interns under the same school regulations.

At the time in which the several tests were done, these students, who came to the Mexico City altitude from all over the country, including sea level, had at least six months in town.

(*) This study was sponsored by the "Fundación para la Investigación Científica" en la Escuela Médico Militar, A. C."

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Received for publication, April 5th, 1959.

None of the observations were made at the basal conditions, but at about the same hour of the day in every case. Some tests were made in the middle of the morning, others in the middle of the afternoon. Sometimes, a test was repeatedly made on the same subject, after a few days intervals, in order to minimize the emotional component of the responses.

The studied changes included: a) heart rate read from E. K. G. records; b) blood pressure, taken by the method employed clinically on patients; c) breathing rate and amplitude by a spirographic method (vital capacity was measured in every case), and d) blood saturation recorded by an oximeter earpiece, Woods type, on a Grass d. c. amplifier and ink galvanometer.

Conditions of hypoxia were accomplished by letting the subject breathe during 4 to 5 minutes in a closed space having 10 liters of capacity (the bell of a spirometer). Carbon dioxide was absorbed by the soda lime in the apparatus. The spirometer used (Siemens Metabolostat), had an inside pumping system to recirculate continuously the gas mixture through the tubes attached at the mouthpiece. This system tends to maintain a constant composition of the gas and, at the same time, to reduce the resistance to breathing.

Breathing into the apparatus was stopped when the subject was feeling a strong sensation of "lack of air", usually when the arterial blood oxygen saturation had fallen to around 78 per cent (75 to 80). At this time, breathing was suddenly shifted to room air. All gas measurements were made at 582 mm Hg barometric pressure, and at room temperature (19-21° C).

The standard practice of letting the subject go up and down a stool, 20 centimeters high, thirty times in a minute, during one minute, was the one selected as physical exercise test. As soon as possible after exercise (around ten seconds) the subjects were made to breathe 100 per cent oxygen.

In both instances, the blood saturation was continuously being measured. The rate of change in arterial blood oxygen saturation was determined as previously described (5). The reciprocal of the time to reach the hundred per cent of the change was determined by extrapolation, by plotting on semilog paper the points corresponding to 25, 50, 75 and 90 per cent of the change in saturation.

Results

A. *Heart rate variations with hypoxia.* — Heart rate increases as the partial pressure of oxygen in the breathing gas decreases. There are wide individual variations in the rate of this increase. There are some irregularities in its time course which may be of two kinds. One depends on respiratory arrhythmia, present in most of the cases. The other were unpredictable variations. They were sometimes associated with an emotional factor. On occasions, it was possible to correlate them with changes in arterial blood pressure, at times both changing in the same direction, at others, particularly if the blood pressure showed a marked variation, changing in the opposite direction.

Figure 1 (top left) shows the average time course of the heart rate variations during progressive hypoxia. With the averages in per cent of the control values, plotted against oxygen tension in arterial blood, the left hand curve in Figure 2 was constructed with data taken every 30 seconds. It shows that the heart rate has a linear relation with the decrement in oxygen tension of arterial blood, at least, for the range explored, and for that rate of change

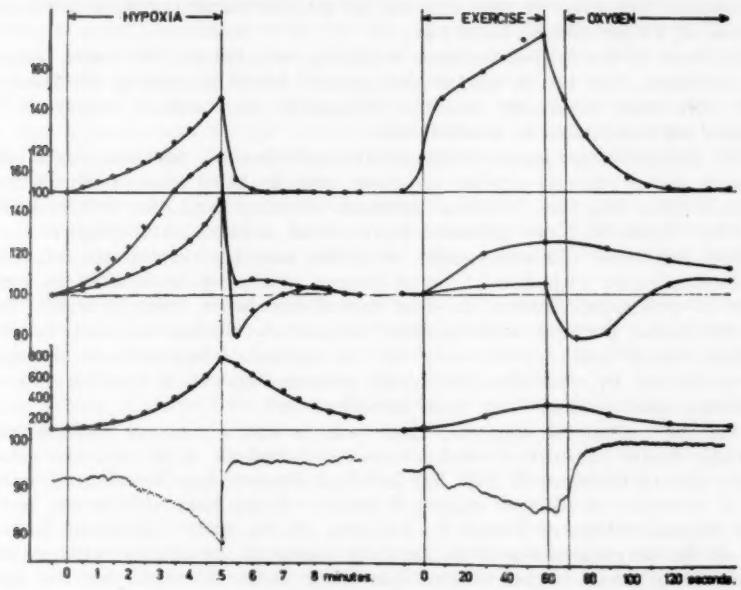

FIG. 1.—*From top to bottom temporal course of heart rate, systolic (dots) and diastolic (crosses) blood pressure, ventilation and arterial blood oxygen saturation. During and after hypoxia on the left, and during and after exercise on the right. Ordinates for each curve: values in per cent of the controls. The points represent averages of all the observations. The saturation curves are the originals from a typical example. Abscissae: Time, in minutes for the left side curves; in seconds for those at the right.*

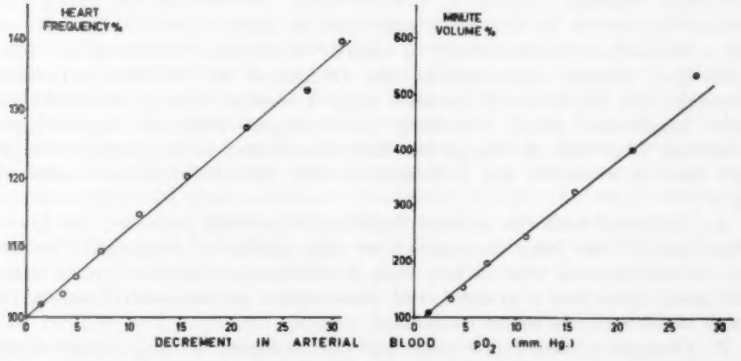

FIG. 2.—*Relation between changes in heart rate (left) and changes in pulmonary ventilation (right) with the partial oxygen tension in arterial blood (abscissae). The values at the ordinates are percentual averages of all the observations.*

in hypoxia. For every 8 mm Hg fall in arterial oxygen tension there is an increase of 10 per cent in heart rate.

As soon as the subject switches breathing to room air, the heart frequency also decreases, but not as fast as the arterial blood saturation increases. The wide individual variations made it impossible to correlate accurately both changes for this return to control level.

B. *Arterial blood pressure changes during hypoxia.* – Systemic arterial blood pressure shows changes similar to those seen in heart rate. With increasing hypoxia there is a rise in blood pressure, affecting both the systolic and the diastolic. Diastolic blood pressure increases at a faster rate (Figure 1). The method employed did not permit to make accurate correlations of changes in blood pressure with arterial blood oxygen saturation or tension. In general, there is a similar relation to that found for heart rate, between systolic arterial blood pressure and oxygen tension. A similar relation holds for diastolic blood pressure, but only for low values of hypoxia. At the end of the period of hypoxia diastolic blood pressure showed a tendency to reach a plateau and, in some cases, even started to fall.

At the release of hypoxia, there was a fast return to normal values. Diastolic blood pressure showed always an overshoot of an average value of 20 per cent of the control. This fall in blood pressure lasts for about 2 minutes.

C. *Ventilatory changes during hypoxia.* – Pulmonary ventilation increases with hypoxia (Figures 1 and 2). In spite of the wide individual variations and of the irregularities seen in the time course of the change with increasing degree of hypoxia, it can be said that there is no threshold for the change. In support of this statement is the observation that ventilation showed a significant decrease below the resting values when the subject was made to breathe pure oxygen.

As the curve at the right in Figure 2 shows, ventilation increased linearly with the calculated oxygen tension in arterial blood. Roughly, for every 6 mm Hg fall in oxygen tension there is an increase in ventilation equal to 100 per cent.

D. *The saturation changes during and after hypoxia.* – During rebreathing, the arterial blood oxygen saturation fell gradually, very slowly at the start and faster every minute (Figure 1, bottom left). At the end of the period of hypoxia, the return to normal is very fast. It takes usually 0.1 or 0.2 sec to reach a maximum which usually is slightly above the resting value. The rate of this last change, expressed as the reciprocal of the time to reach an asymptote, was significantly greater than a similar change recorded at the control conditions while breathing pure oxygen with the same degree of ventilation. This rate of change has been considered to be proportional to the lung's surface available for diffusion, or the functional surface area of the lung (4).

As compared with the control figure, taken as 100 per cent, the functional surface area of the lung increases after that period of hypoxia. The average value of this increase was of 135, with a standard deviation of plus minus 38. With time, there was a gradual and slow return to the control values, taking from 5 to 10 minutes to be completed.

E. *Changes in heart rate with exercise.* – Figure 1 (top right) shows the changes in heart rate during exercise. This curve, as well as all the others excepting the saturation curves at the bottom, was plotted with the average percentual values from all the observations. Compared with the changes during

hypoxia in can be seen here that, there is a much faster rate of variation, and that there is no good correlation with the fall in arterial blood oxygen saturation. This fall was usually small, amounting to about 3 to 4 per cent of the basal values and, in general, it showed many irregularities in its time course.

The return to the basal values after exercise was similar than the return after the hypoxia test. In the present observations no attempt was made to follow accurately the time course of this return, as very soon the subjects were made to breathe pure oxygen.

Before the exercise test, when the subject is said what he is going to do, there is a definite increase in heart rate amounting to 10-20 per cent of the basal value. If the exercise was not made, this increased heart rate persisted for two or three minutes.

F. *Blood pressure changes with exercise.* — Arterial blood pressure changes during exercise showed also some differences when compared with those seen in hypoxia. Systolic blood pressure increased at a faster rate. Diastolic pressure showed a definite slower rate of increase. After exercise, there was a slower gradual return of the systolic values, this being completed after about 5 minutes. Diastolic blood pressure also showed a fall of shorter duration, less than one minute, followed by a second rise with a gradual coming back to previous levels. These blood pressure changes showed the same pattern even if the exercise was not followed by the period of oxygen breathing.

G. *Ventilation changes with exercise.* — Pulmonary ventilation increased during exercise but with irregularities and wide individual variations. The known increase when the subject received the order for exercise was seen before he made any actual movement. The maximal value reached with exercise was as an average of 332 per cent, with a standard deviation of 130. The return to the basal condition was much slower. Five minutes after exercise, ventilation was still increased 36 per cent, as an average.

H. *Blood saturation changes during and after exercise.* — In many cases, a slight fall in saturation, of about 2 per cent was recorded at the time of the order of doing exercise and before doing any actual movement. This fall could be seen even if the ventilation showed an increase, provided it was not too great. During exercise, there was, generally, a more important gradual fall (Figure 1, bottom right) with some irregularities. After exercise, the rate of increase in saturation when breathing pure oxygen was definitely slower compared with the controls for the same degree of pulmonary ventilation. The average value found was of 64 per cent, with a standard deviation of 21.

I. *Physical characteristics of the studied subjects.* — Even if the studied young men constituted a rather homogeneous group, there were important individual variations between them. In table I are summarized some of the values obtained with their standard deviations. Those who were coming from sea level did not give significantly different values from the average.

Some other data recorded were as follows: average breathing frequency at rest, 13.58 ± 0.32 liters, per minute, per square meter body surface.

The heart rate showed a significant slowing when breathing pure oxygen (Table I). The arterial blood oxygen saturation is smaller than that reported at sea level, 92.6 ± 1.9 per cent. It is important to note that only in very few cases, and for short periods of time, it keeps a constant value. It is continuously changing following the irregularities in breathing. In some cases, when breathing is slow, the records show the waves corresponding to every

respiratory movement. Excitement or any other emotional state manifest in the records usually by a fall in saturation. We have already described the one accompanying the excitement due to the idea of doing exercise.

Discussion

In the previous paper mentioned, García Ramos (4) had assumed that circulatory and respiratory adaptations during hypoxia were equivalent to those during physical exercise. That assumption was postulated only for the purpose of study of the respiratory function during conditions of maximal demands from the organism. It was supposed that, apart from the increased ventilation, the high cardiac output during hypoxia would bring the opening of most of the alveolar capillaries and produce a state of maximal diffusing area in the lung for gas interchange. This idea did not take into account the possible vascular reactions and their importance under different conditions. It is not surprising, therefore, that the data presented in this paper did not fully support that assumption.

Figure 1 shows that the circulatory adaptations in those two conditions studied are similar, but with important quantitative differences. These are differences which may be attributed to the different situation of the pulmonary circulation in each case. In the first place, we may admit that the changes in heart rate and in systemic arterial blood pressure are an index of increased activity of the sympatho-adrenal system. For the purpose of the present discussion we are not going to consider the decrease in tonus of the parasympathetic system, as the effects are in the same direction. Secondly, we have to admit that sympathetic activity is a phenomenon which involves the whole system (2). Third, that sympathetic actions are going to affect in the same direction the systemic and the pulmonary circulations (6). Therefore, all the observed changes will be the result of this increased sympathetic activity, more or less modified by the following factors. a) The change itself, for example, a high blood pressure affecting reflexly the heart rate. b) Parasympathetic activity affecting the heart and the pulmonary vascular system. c) Vasodilatation of muscle vessels during activity. d) The general vasodilating effect of hypoxia. e) The general vasodilating action of metabolic products of muscle activity.

We know that during physical exercise, the increased sympathetic activity results from a psychical factor and from a series of reflexes, particularly those initiated within the active muscles. This, together with the increased venous return would be the mechanism for the observed increase in cardiac output (3, 7). More blood entering into any vascular system would induce a rise in blood pressure if the arteriolar output into the capillary bed does not increase at the same time. If this happens, the rise can be more or less compensated. This is what probably happens in the systemic circulation through the vasodilation which occurs in active muscles, in spite of the general vasoconstrictive action of sympathetic activity. In the pulmonary circulation this compensatory factor does not exist. In fact, a rise in pulmonary arterial pressure during exercise has been reported. This rise, even if of a small magnitude, has great significance if it is considered that the vascular bed of the lung normally presents a very low resistance to flow. The vasoconstriction in the lung affects mainly the respiratory vascular system (6). This is the reason for the observed fall in arterial blood oxygen saturation previous to and during exercise. At the end

of the exercise period, this vasoconstriction would be the more important persisting change. In fact, the functional surface area of the lung decreases in size, as revealed by the slower rate of change in arterial blood oxygen saturation (Figure 1; Table I).

TABLE I

	At rest		Hypoxia maximal value	Exercise maximal value
	Air	Oxygen		
Heart rate, beats/min.	71 ± 9	68 ± 6	103 ± 21	124 ± 16
Systolic blood pressure	103 ± 10	103 ± 10	152 ± 18	134 ± 14
Diastolic blood pressure	66 ± 9	65 ± 8	111 ± 23	69 ± 11
Ventilation l/min/m²	4.2 ± 0.9	3.8 ± 0.8	33.5 ± 6.2	13.9 ± 5.1
Functional surface area of the lung, per cent	100 ± 24		135 ± 38	64 ± 21

Arterial blood pressure in millimeters of mercury. The values for functional surface area are expressed in per cent of the value obtained at rest; deviations for the value at rest are from the average for all the observations.

This might be true only for a short period of physical exercise, as is the one studied here. It is probable that for longer or stronger exercise tests, some other factors, as the vasodilating actions of carbon dioxide and other products of muscle activity, or the reduction in sympathetic activity, or the increase in tonus of the parasympathetic system, may come to complicate the picture.

During hypoxia, very different and complicated mechanisms come into play to produce an increase in activity of the sympatho-adrenal system. An excitatory action on the central nervous system, involving hypothalamic, mid-brain and spinal cord centres; a direct action upon the adrenal medulla with liberation of adrenaline; a direct action upon the heart; indirect effects via chemo-receptor mechanisms, etc.

In the first stages of hypoxia, the increased sympathetic activity is not compensated by any vasodilatory effect. The rise in blood pressure, both systemic and pulmonary, will tend to be more important than in exercise, particularly for the values in diastolic blood pressure. The ratio between heart rate and systolic arterial blood pressure (percentual values) has at any moment during hypoxia a value near unity. It is less than one (0.8-0.9) if the value of the diastolic blood pressure is taken. This same ratio has a value of about 1.33 during exercise when the figure of systolic arterial blood pressure is taken, and of about 1.66 for the diastolic values.

Gradually, with increasing degree of hypoxia, the vasodilating effect of anoxia itself is becoming apparent. The relation between heart rate and diastolic arterial blood pressure tends to increase. This effect would be the one revealed at the end of the hypoxial period by the fall in diastolic systemic arterial blood pressure. The pulmonary vascular system would probably be affected in greater proportion. After hypoxia, the functional surface area

of the lung increases, as is shown by the faster rate of change in arterial blood oxygen saturation (Figure 1; Table I).

Two conclusions can be reached from the present results.

1) Hypoxia is a better test for the study of respiratory reserve involving the functional surface area of the lung. In this case, the cardiac output is largely increased and the vasodilation produced in the respiratory vascular system by the low oxygen gas mixture breathed, will produce an optimal adaptation of the circulation of the lung to the respiratory function. It is possible that in some cases the vasoconstriction due to sympathetic activity could be important. In fact, there were some subjects in whom the functional surface area of the lung showed after hypoxia a smaller value than that of the control.

2) During exercise, the uncompensated vasoconstriction in the respiratory vascular system of the lung makes a poor adaptation of the organism for the exaggerated demands. This observation, however, is in accord with those of Lammerant (8) who has recently reported a decrease in the amount of blood in the lung during exercise. There are some practical observations showing that this poor adaptation does occur during the first phase of exercise, and that it is more clear in untrained subjects. Later in exercise the opposite is seen, an increase in the functional surface area of the lung. This could be related to the so called "second wind" and probably due to the decrease in sympathetic tonus and to the vasodilatory action of the products of muscle activity.

With respect to the physical characteristics of the subjects studied, the different values determined do not show significant deviations from those reported for young men at sea level (1, 10). This may be the result of other changes taking place during acclimatization. Vital capacity was smaller than that reported by other investigators, both when taking it as a function of body surface (11) or when relating it mainly to height (1, 10).

Arterial blood oxygen saturation has lower values than those reported at sea level. Pulmonary ventilation, however, does not seem to be higher. It is important to note that ventilation did show an increase since the beginning of hypoxia (Figures 1 and 2). This, and the fact that ventilation is reduced when breathing pure oxygen, suggests that the mechanism responsible for the adaptation of ventilation to hypoxemia, in all probability the chemoreceptors, is active under normal conditions.

Summary

Heart rate, systemic blood pressure, pulmonary ventilation and arterial blood oxygen saturation were determined at rest, during pure oxygen breathing, during and after a period of hypoxia by rebreathing, and during and after a standard exercise test.

The recorded changes in systemic circulation suggest that circulatory adaptations for the respiratory function of the lung, are not the same in the lesser circulation during hypoxia and during exercise. Cardiac output would be increased in both conditions, but the actual amount of blood coming in contact with alveolar air would be increased after hypoxia and decreased after exercise. These conclusions are based on the observations that the rate of change in arterial blood oxygen saturation is faster than the control after hypoxia, and slower after exercise. Possible involved mechanisms are discussed.

It is concluded that for the study of respiratory functional reserve, hypoxia is a better test than exercise, since circulatory adaptations to respiration are optimal in the first condition.

Resumen

En 50 individuos jóvenes, todos sujetos a condiciones de vida semejantes, se estudió la frecuencia cardíaca, la presión arterial, la ventilación pulmonar y los cambios en la saturación de oxígeno de la sangre arterial en condiciones de reposo, respirando oxígeno puro, durante y después de un período de hipoxia y durante y después de una prueba de ejercicio físico. La velocidad de cambio en el grado de saturación al pasar de una baja a una alta tensión parcial de oxígeno en el aire inspirado, en función de la ventilación pulmonar en esos momentos, se tomó como índice de la magnitud del área pulmonar funcional para intercambio gaseoso.

Los cambios registrados en la circulación general sugieren que las modificaciones circulatorias que ocurren en el pulmón no son las mismas para los grados de hipoxia y de ejercicio físico estudiados. Después de la hipoxia, sería predominante un estado de vasodilatación en el sistema vascular respiratorio. Durante y después del ejercicio, la vasoconstricción en ese mismo sistema vascular sería la regla. Estos cambios, determinando la cantidad de sangre que se pondría en contacto con el aire alveolar, darían un aumento del área pulmonar funcional con la hipoxia, y una reducción de la misma con el ejercicio.

Se concluye que para el estudio de la capacidad funcional de reserva de la respiración, es mejor hacerlo en condiciones de hipoxia que durante o después de ejercicio físico. Las adaptaciones circulatorias en el primer caso, son óptimas por lo que al intercambio gaseoso se refiere.

Las características físicas de los sujetos estudiados a la altura de la ciudad de México (2268 metros sobre el nivel del mar), no difieren mucho de las comunicadas por otros investigadores para las condiciones al nivel del mar. La saturación de oxígeno en la sangre arterial es, sin embargo, más baja (92.6 ± 1.9). Los valores de la capacidad vital muestran también cifras inferiores, tanto en función de la talla, como de la superficie corporal.

Las variaciones de la ventilación desde los primeros momentos de la hipoxia, y el hecho que ésta se reduzca al respirar oxígeno puro, apoyan la idea que los mecanismos operantes responsables de la regulación de la ventilación pulmonar, o sea, los quimio-receptores, están activos en condiciones normales.

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THE INITIATION OF ACTION POTENTIALS AT PACINIAN CORPUSCLES

R. Álvarez Buylla and J. Remolina

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In a previous publication, Álvarez-Buylla and Ramírez de Arellano (1) have shown that the initiation of a nerve impulse at the Pacinian corpuscle is preceded by the development of a local potential which corresponds to activity of the axon membrane within the Pacinian corpuscle (2). These findings have been confirmed by Gray and Sato (3), Loewenstein and Altamirano-Orrego (11) and Loewenstein (12, 13, 14). The features of this depolarization of the nerve membrane are similar to those of the local responses studied by Katz (9, 10) and Hodgkin (7) in unmyelinated fibers and by Rosenblueth and Luco (15) in myelinated mammalian axons.

Very little is known about the relationship between these local potentials of the corpuscles and the characteristics of the mechanical stimuli which originate them. For this reason it is difficult to explain why there is no propagated response when a slowly increasing mechanical stimulus is applied. The lack of response to such a stimulus might be due to the local depolarization being insufficient to originate a propagated response.

On the other hand, in accord with Hill's theory of excitation (6), with a slowly rising stimulus the local response may reach values even greater than those produced by rapid stimuli, but because of rise of the threshold due to accommodation, the "local potential" does not reach thereshold values and therefore does not give rise to an action potential.

A similar problem arises also in relation to the process of adaptation. In fact, the repetitive responses originated by a "rectangular" mechanical stimulus cease in receptors of rapid adaptation about 100 msec. after the beginning of the stimulus, whereas in other receptors of slow adaptation, the responses continue for many seconds. If the repetitive responses are originated by a local

Received for publication, April 5th, 1959.

depolarization, the problem arises whether a local response is maintained at a constant level during the time of repetitive activity of the receptor or whether these repetitive responses are due to oscillatory local responses.

Finally, if we attempt to measure the excitability of Pacinian corpuscles using their physiological stimulus, that is, the mechanical stimulus, we should know whether the stimulating factor is the pressure exerted or the time through which the pressure is maintained, which would correspond in electrical stimulation to the intensity multiplied by the duration of the stimuli. Again, the stimulating factor might be the rate of development of the pressure applied to the corpuscles (first derivative) or the changes of this rate (second derivative).

In order to obtain data bearing on these problems, this study was carried out, recording simultaneously different stimuli and the local potentials which they produced. The experiments were performed on the preparation of the isolated receptor and nerve fiber of the cat's mesentery previously described (1).

Methods

All the experiments were acute. The corpuscles were excised from cats anesthetized with 40 mgr. of sodium pentobarbital per kg. of body weight. The Pacinian corpuscles selected were those located at some distance from the neurovascular bundles within the mesentery or the mesosigmoid. The axon attached to these corpuscles travels for a relatively long distance without mixing with other nerve fibers, thereby making it possible to place easily 5 electrodes

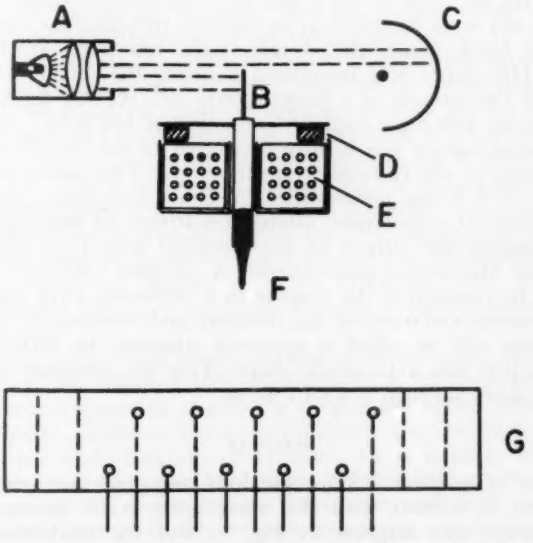

Fig. 1.—*SCHEMA OF THE APPARATUS FOR MECHANICAL STIMULATION. A, source of light. B, screen that interrupts the light rays. C, photoelectric cell. D, foam rubber cushions. E, coil. F, bakelite stem which applies the mechanical stimulus to the corpuscle. G, lucite plate with 10 platinum electrodes, on which the preparation is placed.*

at intervals of 5 mm. along this single nerve fiber. In addition, in most experiments the nerve trunk joined by the axon was included in the dissection. In this way a preparation was obtained consisting of the Pacinian corpuscles, its nerve fiber and a certain length of the nerve trunk, having a total length of approximately 5 cm. The preparation was laid on ten platinum electrodes fixed on a plastic base (Fig. 1 G). It was submerged in mineral oil. In order to fix the Pacinian corpuscle, a small strip of mesenterium was left, attached to the corpuscle at the pole opposite to the emergence of the nerve fiber. The corpuscle was placed on a cork plate.

Mechanical stimulation was carried out by means of an electromagnetic stimulator. It consists of a coil (Fig. 1 E) having a resistance of 1,000 ohms, placed inside an iron box. Through the center of this coil passes a metal tube, polished and adjusted to permit vertical movements with a minimum friction. At the lower opening of this tube there is a plastic piece (F) having at its lower end a blunt point which is applied to the corpuscle. At the other end of the tube a thin iron disk is attached, which closes the electromagnetic field. This disk is separated from the box by three small rubber-sponge cushions (D) attached with plastic cement to the box and to the disk. This mechanical stimulator does not present practically any limitations with regard to the intensity of the stimuli, and the time course of the latter is not affected by the greater or smaller pressure which is applied to the corpuscle. The time constant is around 0.9 msec.

There is a linear relation between the acceleration of the rod of the stimulator during the first millisecond and the voltage applied to the coil, if the shape and the duration of the pulses are maintained constant. The intensity of these pulses can serve therefore as an indirect indicator for the stimuli.

A strip of black paper (B), 3 mm. high, was fixed at the top of the metalic disk. This paper was interposed between the source (A) of parallel-beam light and the cathode of a photoelectric cell (C, 929 RCA). The output of this cell was fed into a preamplifier consisting of two 6 SK 7 tubes connected as a bridge, whose output was in turn connected to the circuit controlling one of the two beams of the cathode-ray oscillograph. The action potentials were amplified by a P 4 Grass preamplifier. A Grass stimulator (model S 4) was used for the electrical stimulation. Mechanical stimuli of rectangular form were obtained by feeding the output of the electrical stimulator into the electromagnetic device. Mechanical pulses having a constant velocity of displacement were obtained by connecting the magnet to a saw-tooth wave generator, which permits independent variations of the intensity and duration of the waves. This form of stimulus will be called a saw-tooth stimulus. In certain experiments the stimuli applied had a parabolic shape. This was obtained by multiplying two saw-teeth pulses through a 6 SA 7 tube.

Results

A. *Mechanical artifacts.* — Since the local responses are recorded with an electrode placed in contact with the nerve fiber at its emergence from the Pacinian corpuscle (see diagram in Fig. 2), and the mechanical stimulus is applied to the corpuscle, there is the possibility of originating artifacts due to movement. These artifacts might interfere with the recording of the local responses. Care was taken to minimize these possible artifacts. Figure 2 A shows the local response produced by a brief mechanical stimulus of low intensity.

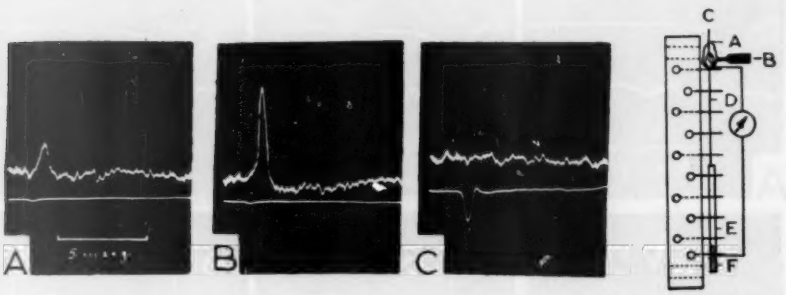

FIG. 2. — *MECHANICAL STIMULATION OF A PACINIAN CORPUSCLE. Upper tracing, monophasic recording at the point were the axon emerges from the corpuscle; lower tracing, photoelectric recording of the mechanical stimulus applied. In A, local response to a brief stimulus of small intensity. In B, the intensity of the stimulus was slightly increased and the action potential emerged. Between B and C a drop of ether was applied to the corpuscle. In C, a stimulus 30 times larger than that of A did not produce any alteration in the recording of the fiber's activity. To the right, diagram of the experiment: A, strip of mesenterium; B, plastic tip of mechanical stimulator; C, Pacinian corpuscle; D, isolated fiber; E, whole nerve; F, crushed region.*

A minimal increase in the intensity of this stimulus produced the action potential illustrated in B. Between B and C, without any other change, a drop of ether was applied to the corpuscle. A mechanical stimulus, applied in C, in spite of having an intensity 30 times greater than in B does not produce practically any alteration in the electrogram.

B. *Effects of mechanical stimulation of the Pacinian corpuscles with stimuli of two milliseconds duration and of variable intensities.* — The responses obtained by applying to the Pacinian corpuscle brief mechanical stimuli whose intensity is progressively increased are illustrated in Figure 3. In A a double disturbance is noticeable, consisting of two negative local responses. In B the second response is more ostensible; in C it is just subthreshold for the spike potential; and in D this second local response originates an action potential. The first response did not reach the necessary magnitude to give rise to a propagated action potential until a much stronger stimulus was applied (E). At this moment the second local response, which had reached in D the threshold value, ceased to give a propagated response, because it appeared during the refractory period produced by the first response.

In Figure 3 E a late third local response develops more than 8 msecs. after the application of the stimulus; in F the intensity of the stimulus was sufficient for the third local response to originate a propagated action potential.

C. *Rectangular stimuli.* — Figure 4 illustrates the responses to mechanical rectangular pulses with duration of 10 msec. In A a pulse of low intensity initiates a local response at the beginning of the stimulus; this response lasts about 3 msec. In B this local response is clearer; and in C, with a stimulus somewhat stronger than in B, this response originates a propagated spike.

In D, three additional local responses are observed and at the "off" of the stimulus a second action potential is produced. The third local response develops 7.6 msec. after the first spike. A small increase of the intensity of the stimulus produces an additional propagated response (E). The local response

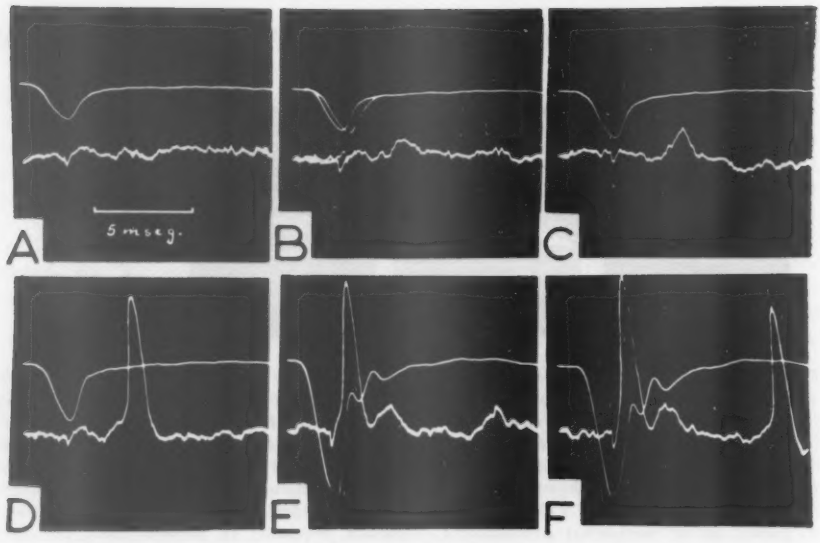

FIG. 3. — *MECHANICAL STIMULATION OF A PACINIAN CORPUSCLE, WITH STIMULI OF 2 MILLISECONDS DURATION, AND OF INCREASING INTENSITY. Paper tracing, photoelectrical recording of the stimulus. Lower tracing, monophasic recording of the axon's electrical activity at the point were it emerges from the corpuscle. Time: 5 milliseconds. Other explanations in the text.*

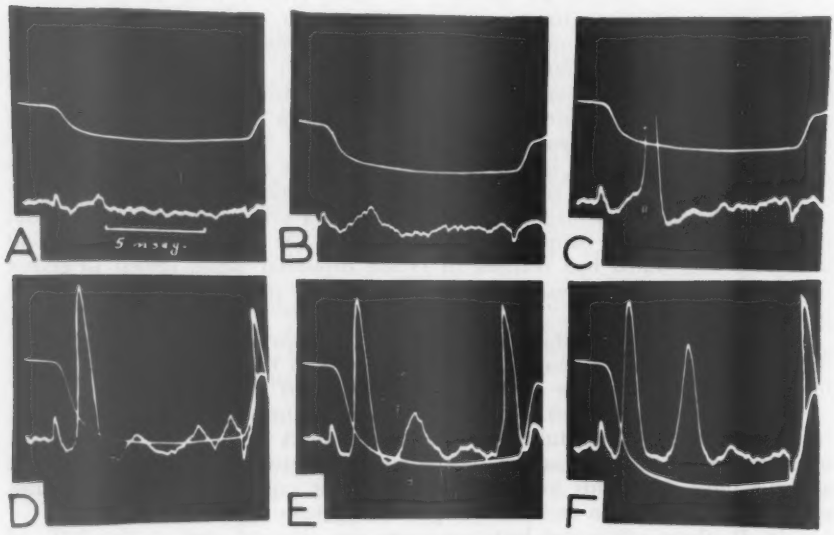

FIG. 4. — *MECHANICAL STIMULATION OF A PACINIAN CORPUSCLE WITH RECTANGULAR STIMULI OF 10 MILLISECONDS DURATION AND OF INCREASING INTENSITY. Upper tracing, photoelectrical recording of the stimulus. Lower tracing, monophasic recording of the axon's electrical activity at the point where it emerges from the corpuscle. Time: 5 milliseconds. Other explanations in the text.*

that takes place at 2.6 msec. after the first spike is not able to initiate a propagated response in spite of reaching a considerable size. When the intensity of the stimulus is increased further, this local response originates a spike potential of lower voltage, because it develops during the refractory period (F).

In these records one can observe that the depolarization phase of the local response becomes steeper as the intensity of the stimulus increases. In all the cases however, after reaching its maximum, it returns to the baseline following an approximately exponential time course. The time constant of this exponential in our experiments was about 0.5 to 0.8 msec. Gray and Sato (3) observed the same fact, giving an average of 1.7 msec. for this time constant.

D. *Stimulating with "saw-teeth" pulses.* — Figure 5 shows the results obtained with lineally increasing mechanical pulses. The duration of each pulse is 10 msec.

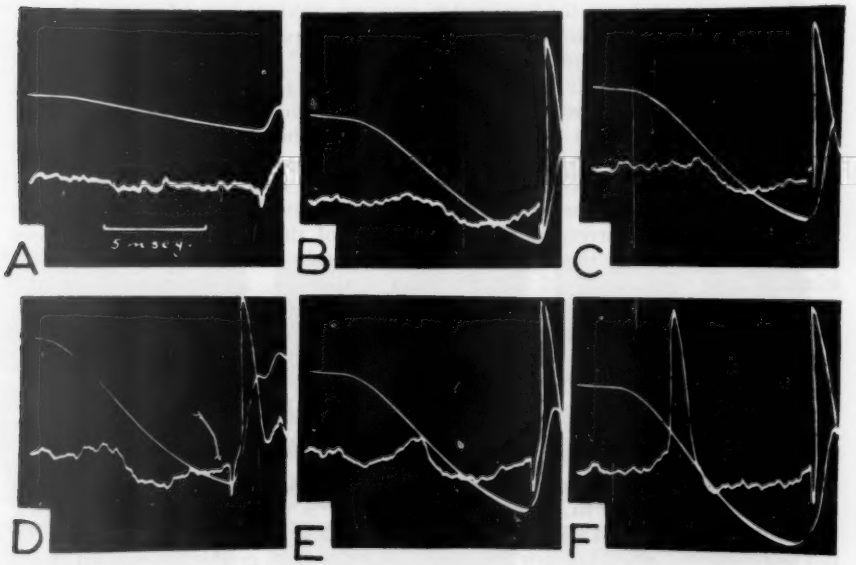

FIG. 5. — *MECHANICAL STIMULATION OF A PACINIAN CORPUSCLE WITH SAW-TEETH STIMULI OF 10 MILLISECONDS DURATION AND OF INCREASING SPEED AND INTENSITY. Upper tracing, photoelectrical recording of the stimulus. Lower tracing, monophasic recording of the axon's electrical activity at the point where it emerges from the corpuscle. Time: 5 milliseconds. Other explanations in the text.*

An increase of intensity means an increase of the speed with which the pressure is applied to the corpuscle. In A a stimulus of low speed produced a slight lowering of the baseline, that is, a positive potential, which increased gradually in B, C and D, as the stimuli were intensified. This positive potential reveals a hyperpolarization of the membrane and lasts more than 7 msec. In E, when the stimulus was increased further, there appeared a negative potential superimposed on the first half of the positive potential. This negative potential corresponds to that which appeared with the other forms of stimuli, as described

above, and is interpreted as the local response of the intracorpuscular axon. In F the negative local response gave rise to an action potential. The positive potentials, which we shall call "positive local responses", have a duration more than twice that of the negative local responses.

E. *Superposition of brief (2 msec.) to long (10 to 20 msec.) mechanical stimuli.* — The threshold of the receptor to the long and to the brief mechanical stimuli was first determined. The long pulses were then applied with an intensity of about 0.3 threshold and the threshold for the brief stimuli delivered at different times was observed. These short pulses had both polarities, i. e., they either compressed or decompressed the corpuscle.

The results were qualitatively uniform. The threshold to the brief stimuli was lowered during the development of the negative local responses to the long pulses, and was raised during the appearance of the positive local responses.

In some experiments the long pulses were saw-teethed instead of rectangular. A decrease of threshold was observed during the first 5 msec. and an increase during the following 5 msec. (Fig. 6 D and E).

With the rectangular pulses of 20 msec. duration a constant phase is observed, when the pressure exerted by the mechanical stimulator on the corpuscle is maximal, but without variations, and therefore unable to produce propagated responses. If during the course of this phase a variation is produced, whether positive or negative, by the addition of a 2 msec. stimulus, propagated responses appear. The periods of greater excitability to electric as well as to mechanical stimuli, corresponded to the peaks of the local negative responses (Fig. 7). Thus, during the application of saw-tooth or rectangular mechanical stimulus, the excitability of the Pacinian corpuscles, as determined by the threshold to brief electrical or mechanical stimuli, shows variations which are parallel to the time course of the local responses. The excitability is increased during the development of the negative local responses, and decreased during the development of the positive ones.

Discussion

Threshold of the Pacinian corpuscle to mechanical stimuli. — If we compare the records illustrated in Figure 6 A and B it is clear that the stimulating factor during mechanical stimulation of the Pacinian corpuscles, is not the intensity of the stimulus nor its duration, nor the product obtained from multiplying intensity by duration. A brief and weak stimulus in Figure 6 A evokes a response while a stronger stimulus and of longer duration, in B does not elicit one; it was necessary to increase the intensity of the saw-tooth in B to more than double in order to evoke a response (Fig. 6 C).

The stimulating factor is again not the rate of change of pressure (that is the first derivative of displacement with regard to the time), since the angle between the baseline and the rising phase of the brief stimulus that evokes a response in Figure 6 A is of 23°, and the corresponding angle for the saw-tooth stimulus which did not evoke a response, in B was of 30°; in order to evoke a response it was necessary to increase the speed until the record of the stimulus in C made an angle of 60° with the bascline.

A momentary interruption of a saw-tooth stimulus which is incapable of eliciting a propagated response (Fig. 6 B), by applying a brief stimulus of opposite polarity, which slows, stops or reverses the downward movement of the stimulator,

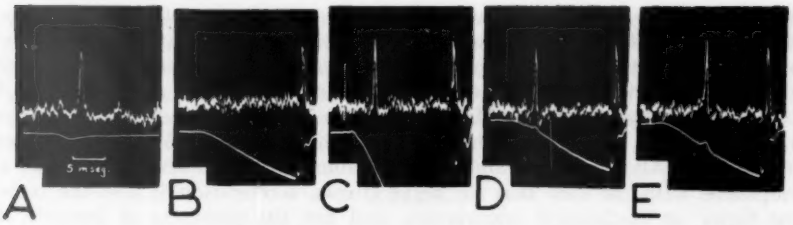

FIG. 6.—*MECHANICAL STIMULATION OF A PACINIAN CORPUSCLE WITH STIMULI OF DIFFERENT FORMS AND INTENSITIES. Upper tracings, monophasic recording of the axon's electrical activity at 7 mm of its emergence point from the corpuscle. Lower tracings, photoelectric recording of the stimuli. A, stimulus of 2 milliseconds duration and threshold intensity. B, stimulation with saw-teeth pulses of 20 milliseconds duration and below threshold intensity. C, the same stimuli with threshold intensity. D, a stimulus of 2 milliseconds duration and opposite polarity is added to the saw-tooth stimulus 3.85 milliseconds after its initiation. E, the same superposition as in D, but at 8.8 milliseconds. Time: 5 milliseconds. Other explanations in the text.*

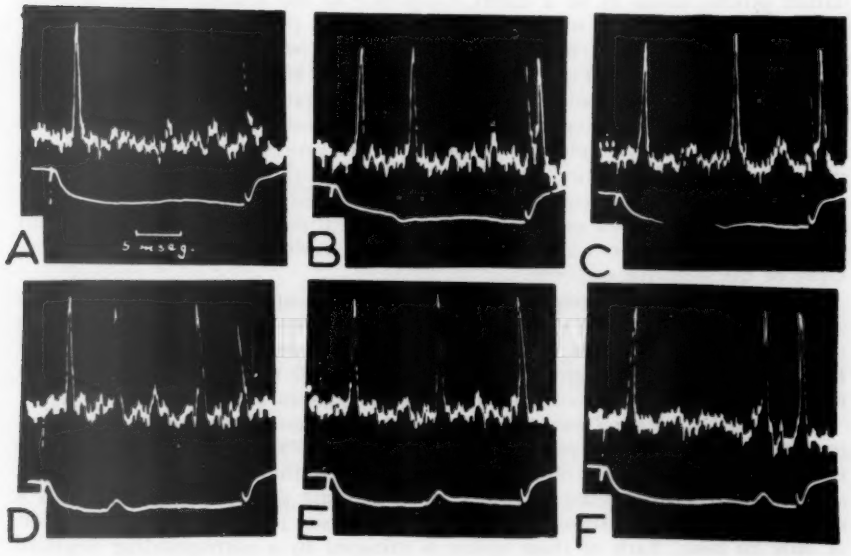

FIG. 7.—*SUPERPOSITION TO A "RECTANGULAR" MECHANICAL STIMULUS (20 MILLISECONDS DURATION) OF ADDITIONAL 2 MILLISECONDS STIMULI OF THE SAME POLARITY IN B AND OF OPPOSITE POLARITY IN D, E AND F. Upper tracing, monophasic recording of the axon's electrical activity at 7 mm of the emergence point from the corpuscle. Lower tracing, photoelectric recording of the stimuli. Time: 5 milliseconds.*

results as shown in D and E, in the initiation of propagated responses. These results indicate that the mechanical stimulation of the Pacinian corpuscle is a consequence of the acceleration of the mechanical pulse; the corpuscle is sensitive to changes in pressure, rather than to constant pressure, as was suggested by Katz (7, 8) and by Gray and Malcolm (4). It is interesting to point out that, in a study of the effects of mechanical pulses on the peroneal nerve of the cat, Rosenblueth, Álvarez-Buylla and García Ramos (16) obtained results that are compatible with the idea that for nerve trunks, acceleration is also the important factor in mechanical stimulation, and not the products of intensity by duration. In other words, in constrast with electrical stimuli, brief mechanical stimuli are more effective than long ones.

In some observations carried out with mechanical parabolic pulses (constant acceleration) with a duration of 20 milliseconds, it was observed that when the acceleration was just threshold, the propagated response appeared at the end of the pulse. When higher accelerations were used the latency for the propagated response diminished accordingly, i. e., the acceleration must act for a certain time in order to be able to stimulate. Our data do not allow us to determine accurately the correlation existing between acceleration and time.

Accommodation of the Pacinian corpuscles to mechanical stimuli. — The accommodation process, considered as a rise of threshold produced by subthreshold stimuli, was observed when saw-teeth pulses were applied. Coincident with this change in threshold, a local positive response appeared. Therefore, the accommodation process seems to be a direct conquence of the stimulus itself, and not of the local potential as suggested in Hill's theory (6).

When the Pacinian corpuscles were stimulated with mechanical stimuli of increasing acceleration (Fig. 5) the first response to develop was a positive potential. As the acceleration increased, a local negative response of increasing amplitude appeared during the first half of the positive response. These facts lead us to suppose that under these conditions two processes of opposite electrical sign develop simultaneously, and that the electrical records correspond to their algebraic sum. The time-course of the positive process is slower than that of the negative. Stimuli of slow acceleration, therefore, exhibit readily the development of the positive process, while those with rapid acceleration favor the development of the negative response.

The positive local responses to mechanical stimulation of the Pacinian corpuscle, appear similar to those found by Rosenblueth and García-Ramos (17) upon electrical stimulation of nerves. According to the theory of Hodgkin and Huxley (8) the positive process might correspond to the outflow of potassium ions, and the negative process to the inflow of sodium ions.

Adaptation of the Pacinian corpuscles to mechanical stimuli. — In a previous paper Álvarez-Buylla and Ramírez de Arellano (1) confirmed the conclusion reached by Gray and Malcolm (4) and Gray and Mathews (5) that the Pacinian corpuscles are fast-adapting receptors, since they are capable of giving up to 8 responses when a brief stimulus of sufficient intensity is applied with a duration of only 20 msec. Each of these spikes is initiated by a corresponding negative local response. In figures 3 and 4 it may be seen that the repetitive negative local responses are separated by hyperpolarization intervals; i. e. the repetitive propagated responses are not originated in the Pacinian corpuscles by a local maintained depolarization, but by oscillatory local responses.

When the pressure is maintained for periods longer than 20 msec the

repetitive responses stop. This may be explained by the fact that the corpuscle is not sensitive to pressure but to acceleration. If the initial acceleration was not able to produce repetitive response, the period of constant pressure will not produce them. When the acceleration is sufficiently intense, even brief stimuli (1 msec) can produce repetitive responses, some of which appear even up to 10 milliseconds after the stimulus has ceased (Fig. 3).

Summary

In the Pacinian corpuscles of the mesentery of the cat the relation between the local responses of the intracorpuscular axon and various forms of mechanical stimuli were studied. It was observed that the stimulating factor is neither the pressure, nor the product of the pressure and the time, nor the speed of the mechanical pulse, but that the adequate stimulus for the Pacinian corpuscles is the acceleration.

In some experiments, a local potential of positive sign was observed, having slower time characteristics than the negative local response.

The threshold of the corpuscle to mechanical and electrical stimuli is higher during the development of this positive local response. It is suggested that this positive potential is the electrical manifestation of the accommodation process of this receptor.

The repetitive propagated responses in the Pacinian corpuscles are originated by oscillatory local responses.

The authors wish to express their sincere appreciation to Dr. Arturo Rosenblueth for his helpful advices in the preparation of this paper.

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THE ACTION OF WEAK HISTOTOXIC HYPOXIA ON ISOLATED NERVE, NEUROMUSCULAR PREPARATION AND SYMPATHETIC GANGLION/NICTITATING MEMBRANE PREPARATION

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INTRODUCTION

IN PREVIOS work, (Russek, 1955 a & b; Russek, 1959 c) it was shown that the intraperitoneal injection of sodium cyanide 0.2 mg/Kg. produced in the unanaesthetized dog a marked tachycardia and a complete inhibition of salivary and motor conditional reflexes. As both effects could be conditioned (could be reproduced by formerly neutral stimuli) it was inferred that both processes should be, at least in part, of reflex nature, but the participation in them of the direct effect of cyanide on peripheral or central structures is unknown. In another paper (Russek, 1959 a), it was seen that the same dose of cyanide injected intravenously, reduced an epileptic electrocortical after-discharge to the 23 % of its control duration. The effect on the EEG was a marked desynchronization (beta activity), similar to that obtained by Dell & Bonvallet (1954) with anoxaemic hypoxia, and demonstrated by these authors to be produced by signals coming from the cardio-aortic and carotid sinus chemoreceptors.

The hypothesis was advanced, that the depression of the epileptic after-discharge could be another manifestation of the reflex inhibition elicited by cyanide on conditional reflexes, but, again, this can not be safely stated without some knowledge about the direct effects of cyanide at the doses used in the preceding experiments.

Some authors describe that cyanide produces impairment of functions (Molnar et al., 1956) and even morphological changes of the CNS (Goslav et al., 1956; Haymaker et al., 1952; Rose et al., 1954; Vosteen, 1956) but all of these authors use doses ranging from 1.5 to 60 mg/Kg.

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Received for publication, April 2nd, 1959.

So, it was thought of interest to study the effect of cyanide upon peripheral nervous structures, as this evidence would give an idea of the direct action of histotoxic hypoxia on nervous tissue, at the small doses that produce central inhibition: If nervous conduction, neuromuscular and ganglionic transmission should be depressed, this direct action should play an important rôle in the observed inhibition.

Methods

Isolated Nerve "in vitro". — In 11 frog and 5 rat sciatic nerves, 63 observations were made, with concentrations of sodium cyanide ranging from 0.002 mg/ml. to 1 mg/ml. The cyanide solutions were made isotonic with NaCl.

The animals were rapidly killed and the sciatic nerve was cut out and laid in a multielectrode nerve box divided in three chambers. The portions of nerve in the two extreme chambers were covered with paraphin oil and the portion in the central chamber with Ringer's solution. The stimulation was made with condensor discharges at 30/s, of sufficient intensity to produce a spike 50 % of the maximal one.

Both stimulating electrodes were placed in one of the side chambers, or the cathode in the central chamber and the anode in a lateral one. The recording electrodes were in the other side chamber. The record was monophasic. The spike was observed in an oscilloscope and its height measured directly in mm. When no changes were observed for 15 min., the Ringer in the central chamber was exchanged with the cyanide isotonic solution, and the changes observed for another 10 to 15 min.

Neuromuscular Preparation "in situ". — In 5 rats anaesthetized with Nembutal (50 mg/Kg.) and 2 cats descerebrated intercollicularly under ether, 34 observations were made, with doses of cyanide ranging from 0.2 to 2 mg/Kg.

Contraction of the gastrocnemius was isotonically recorded in the kymograph. Stimulation of the peripheral end of the sciatic was done under paraphin oil, with condensor discharges at 50/s. and enough intensity to produce a tetanus 50 % of the maximal.

After the tetanus had reached its plateau, the injection of cyanide was done, intraperitoneally in the rats and intravenously in the cats, and the stimulation was continued for 5-10 min.

Superior Cervical Sympathetic Ganglion - Nictitating Membrane Preparation. — In 18 cats, 4 of them anaesthetized (35 mg/kg. w. Nembutal), the rest intercollicularly descerebrated under ether, 100 observations were made, with doses of cyanide from 0.2 to 2 mg/Kg., injected intraperitoneally or intravenously.

The peripheral end of the cervical sympathetic nerve was stimulated under paraphin oil with condensor discharges at 1-5/s. and sufficient intensity to produce a contraction of the nictitating membrane 50 % of the maximal, which was recorded isotonically on a kymograph. The injection of cyanide was applied as soon as the tetanus reached its plateau, and the stimulation continued for another 5-10 min.

Results

A) *Isolated nerve "in vitro".*

Table I shows the effects of four different concentrations of sodium cyanide, in % of the control spike. It is seen that with 0.002 mg/ml., the approximate concentration that will result in the blood after an injection of 0.2 mg/Kg., there is a slight increase of the spike potential.

In the frog nerve the increase is not statistically significant, reflecting the fact that in more than half of the observations there was no observable effect.

The dose of 0.005 mg/ml. (equivalent to 0.5 mg/Kg.) gave no observable effect on frog's nerve and a small decrease on rat's nerve spike. Even a concentration of 0.02 mg/ml. (equivalent to 2 mg/Kg.) gave no significant results, but with a tendency to decrease the spike, and only 1 mg/ml. (100 mg/Kg.) gave a significant depression, almost complete for rat's nerve.

TABLE I

	Frog's sciatic		Rat's sciatic	
mg/ml.	% Change	p	% Change	p
0.002	+ 14.8	0.1	+ 7.8	0.03
0.005	0.0	0.5	— 8.5	0.065
0.02	— 6.2	0.4	—25.0	0.3
1.0	—26.4	< 0.01	—88.5	0.015

B) *Neuromuscular Preparation (sciatic-gastrocnemius) "in situ".*

The results were similar in both, the anaesthetized rats, in which the injections were intraperitoneal and the descerebrated cats in which the injections were intravenous. The doses of 0.2 and 0.5 mg/Kg. produced an increase of the isotonic tetanus, not significant for the smaller dose in the cat (it had no effect in half of the observations) (Table II). The respiration in the cat increased many times during the action of the cyanide (in the rat it was not recorded).

The dose of 2 mg/Kg. that in every occasion produced gasping and stopped the respiration after 2-3 min., produced only a reduction of less than one third in the contraction. Higher doses were not tried because they were lethal.

The latency for the increases in contraction was around 40 sec. for the intravenous injection (while the latency for the respiratory reaction was 5-10 sec.) and around 70 sec. for the intraperitoneal one. The latency for the decrease at 2 mg/Kg. was 140 sec.

C) *Superior Cervical Sympathetic Ganglion/Nictitating Membrane Preparation.*

The effect on the contraction of the nictitating membrane obtained by

TABLE II

	Anaesthetized rat (Intraperitoneal injection)		Descerebrate cat (Intravenous injection)		
mg/Kg.	% Change contraction	p	% Change contraction	p	% Change respiration
0.2	+ 2.3	0.075	+ 5.1	0.2	+ 900
0.5	+ 5.6	0.01	+ 31.0	0.05	+ 1500
2.0	— 27.8	0.06	—	—	—

stimulation of the preganglionic fibres, followed the same pattern of the effect on the nervous spike: an increase with 0.2 mg/Kg., and a decrease at 0.5 and 2 mg/Kg. (Table III). The results were similar with intraperitoneal and intravenous injections, and in the case of intraperitoneal injection, the effect was the same whether the cat was anaesthetized or descerebrated.

TABLE III

	Anaesthetized or descerebrate cat (Intraperitoneal injection)			Descerebrate cat (Intravenous injection)		
mg/Kg.	% Change contraction	p	% Change respiration	% Change contraction	p	% Change respiration
0.1				+ 2.8	0.1	+ 1000
0.2	+ 5.1	0.015	+ 76	+ 19.2	< 0.01	+ 990
0.4				+ 41	0.02	+ 1025
0.5	— 24.4	< 0.01	+ 875	— 32.0	0.06	(Gaspins)
2.0	— 32.6	< 0.01	(Gasping, resp. stops in 1-2 min.)	— 58	0.1	(Gasping, resp. stops in 1 min.)

The average latency of the increase produced with 0.2 mg/Kg. was 90 sec. for intraperitoneal and 24 sec. for intravenous injection. The latency of the decrease at 0.5 mg/Kg. was 130 sec. for intraperitoneal injection and 26 sec. for intravenous. The average latency of the respiratory reaction with intraperitoneal injections was 33 sec. and with intravenous, 7 sec. Moreover, the changes in contraction frequently began when the respiratory reaction was already decreasing.

Discussion

Summarizing the results obtained with the mammalian structures we can say that at the dose of 0.2 mg/Kg. of sodium cyanide there is an increase of the nerve spike, of the contraction of a neuromuscular preparation and of the contraction elicited in the nictitating membrane by preganglionic stimulation.

At the dose of 0.5 mg/Kg. the neuromuscular preparation is still enhanced, but the nerve and the ganglionic preparation are already depressed, the depression being much bigger in the ganglionic preparation. At 2 mg/Kg. all three structures are somewhat depressed. Only at a dose corresponding to 100 mg/Kg. the mammalian nerve is almost completely blocked. The frog's nerve is still more resistant to the action of cyanide.

The increase in height of the nervous spike can be caused either by an increase in conduction velocity of the slower fibres (synchronization) or by a decrease in threshold of fibres not firing before the cyanide. In any case, it can be interpreted as an increase in the excitability of the nerve fibres.

The decrease of the nervous spike that developed at doses of 0.005 mg/ml. or higher, perhaps it is related to the impairment of the sodium pump observed by Hodgkin & Keynes (1953) with concentrations of 0.05-0.5 mg/ml. of sodium cyanide.

The increase in contraction of the neuromuscular preparation caused by 0.2 mg/Kg. could be due to the increased excitability of the nerve, but at 0.5 mg/Kg. this is not possible, because the nerve is already depressed. So, this can only be due to an improvement in neuromuscular transmission, or in muscular contraction. For the purposes of the present work the differentiation between these two possibilities was not important.

The changes in contraction of the nictitating membrane are much bigger than the changes in nerve spike, so, it is likely that they are due to changes in ganglionic transmission. The possibility of changes in the effector muscle was not discarded, but it was not important for the conclusions to be drawn here.

The changes in neuromuscular and ganglionic activity have a much longer latency than the reflex respiratory response. Furthermore, there is not a great difference in magnitude between the effect of intraperitoneal and intravenous injections, on these structures, as there is in their reflex respiratory responses. These two facts are in favor of the assumption that the observed changes in neuromuscular and ganglionic activities, are due to the direct action of cyanide on them, and not a consequence of the reflex mechanisms mobilized by the histotoxic hypoxia.

At the light of the facts presented here it is possible to state that during the strong central inhibition elicited by 0.2 mg/Kg. of cyanide (manifested by a complete disappearance of salivary and motor conditional reflexes and a great reduction in epileptic after-discharges), peripheral nerves, neuromuscular plates and ganglionic synapses are not inhibited at all, but, on the contrary, their excitability is slightly increased. That is, no direct depression of the structures studied is contributing to the muscular and glandular inhibition observed with this dose of cyanide.

The increased excitability of peripheral structures has perhaps the same mechanism to the one in which the stimulation of chemoreceptors is based.

In the work of Ebe (1952) it was shown that a concentration of 0.0025 mg/ml. of sodium cyanide enhances the spontaneous activity of an isolated toad's brain, while 1 mg/ml. blocks it completely. This agrees with the results presented here and suggests that the sensitivity of the central structures to the direct action of cyanide is similar to that of peripheral structures. Of course, further work on mammalian central structures is advisable, but at the present, all the facts point to the conclusion that the central inhibition produced by 0.2 mg/Kg.

of cyanide is entirely of reflex nature, that is, it is caused by the arrival to the centers of signals originated on chemoreceptors. As was pointed out in a previous paper (Russek, 1959 b) it is likely that this inhibition together with "external inhibition" (produced by strong "new" stimuli) is effected through the reticular formation.

Summary

1. — A dose of sodium cyanide of 0.2 mg/Kg. of body weight (or its equivalent "in vitro") produces a slight increase of the spike potential of isolated sciatic nerve, an increase of the contraction of a sciatic-gastrocnemious preparation "in situ" and an increase of the contraction of a nictitating membrane elicited by preganglionic stimulation. It also produces a clear respiratory reaction.

2. — A dose of 0.5 mg/Kg. (or its equivalent "in vitro") produces a small decrease of the mammalian nerve spike and of the nictitating membrane contraction (preganglionic stimulation) but increases the neuromuscular activity. It produces a very strong respiratory reaction, sometimes accompanied by gasping.

3. — A dose of 2 mg/Kg. depresses all three structures and at the same time produces gasping and finally stops respira ion.

4. — A dose of 1 mg/ml. "in vitro" (equivalent to 100 mg/Kg.) blocks almost completely the mammalian nerve spike and reduces to ¾ the frog's nerve spike.

5. — These facts are useful in the interpretation of the central inhibition produced by 0.2 mg/Kg. of cyanide on conditional reflexes and epileptic after-discharges.

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ACTIVIDAD SUBLIMINAL DE LOS QUIMIORREFLEJOS ORIGINADOS POR EL CIANURO DE POTASIO (*)

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En un trabajo previo (Rudomín, Erlij y Eberstadt, [18]) se encontró que la bradicardia producida por la estimulación del nervio depresor aórtico en el conejo aumenta importantemente durante hipoxia o hipoventilación. Varios autores ([13, 23, 24]) opinan que ese aumento de excitabilidad refleja del centro cardioinhibidor se debe a un efecto directo del CO_2 acumulado ([19]). Sin embargo, durante esas maniobras se estimulan importantemente los quimiorreceptores cardioaórticos y senocarotídeos ([14]). Es posible, por lo tanto, como lo sugieren los trabajos de Gellhorn, Cortell y Carlson ([11]) que las descargas quimiorreceptoras modifiquen la actividad refleja de estos centros.

La finalidad de este trabajo fué estudiar la influencia que tiene la actividad quimiorreceptora sobre el centro cardioinhibidor. La actividad de este centro se juzgó en función de la bradicardia producida por la estimulación del nervio aórtico en el conejo ([1, 16, 17]). Los quimiorreceptores circulatorios se activaron selectivamente inyectando pequeñas dosis de KCN ([1, 3, 4, 14, 15]).

Método

Se emplearon 56 conejos anestesiados con pentobarbital sódico (25 a 35 mg por kilogramo de peso por vía intravenosa).

Se abrió el cuello por la línea media y una vez disecada y canulada la tráquea se prepararon ambos depresores de acuerdo con la técnica descrita por Álvarez-Buylla ([1]). Sistemáticamente se disecaron ambos vagos, dejándolos preparados para seccionarlos o estimularlos según fuese necesario.

(*) Este trabajo fué realizado con la ayuda de "Life Insurance Medical Research Fund". Received for publication, April 5th, 1959.

Para registrar la frecuencia cardíaca se colocó un par de electrodos en la región precordial del animal, o directamente sobre el corazón cuando se abrió el tórax. Para registrar la actividad eléctrica del diafragma se colocaron otros electrodos en la inserción xifoidea de dicho músculo. Las señales eléctricas procedentes de estos electrodos se registraron en un electroencefalógrafo (modelo III de Grass). La presión arterial se registró en el cabo central de una de las arterias (femoral o carótida). Como estímulos se emplearon pulsos rectangulares de 1.5 ms de duración provenientes de un estimulador de Grass (modelo S4) y aislados de tierra por una unidad aisladora (S. I. U. de Grass).

El cabo central de los depresores o el periférico de los vagos se colocó sobre electrodos bipolares de plata. Para aislar los electrodos del resto de los tejidos y evitar la desecación de los nervios se cubrieron éstos en todo su trayecto con una capa de aceite mineral.

La intensidad de los estímulos fué siempre 4 veces la que produjo un efecto máximo al estimular el cabo central del depresor a 32/s, o a 5/s el cabo periférico del vago según el caso.

Todos los experimentos se hicieron con respiración artificial. Para inyectar en determinadas zonas se introdujeron catéteres finos de polietileno comprobando su colocación al final del experimento. El resto de los detalles de método se indica en la correspondiente sección de los resultados.

Los cambios de frecuencia cardíaca se juzgaron por el alargamiento porcentual del ciclo cardíaco con respecto a los valores basales.

Resultados

I. — *Efectos producidos por la inyección de KCN y por la estimulación aislada del depresor.* La inyección intraarterial (en la aurícula izquierda o en el tronco braquiocefálico) de 50 a 100 microgramos de KCN produjo una bradicardia con una latencia de 2 a 3 segundos que alcanzó el máximo entre los 6 y 7 segundos. Los efectos obtenidos al inyectar en la vena yugular, aurícula derecha o en la arteria pulmonar, presentaron una latencia mayor (entre los 6 y 8 segundos) alcanzando el máximo entre los 11 y 12 segundos aproximadamente (Fig. 1).

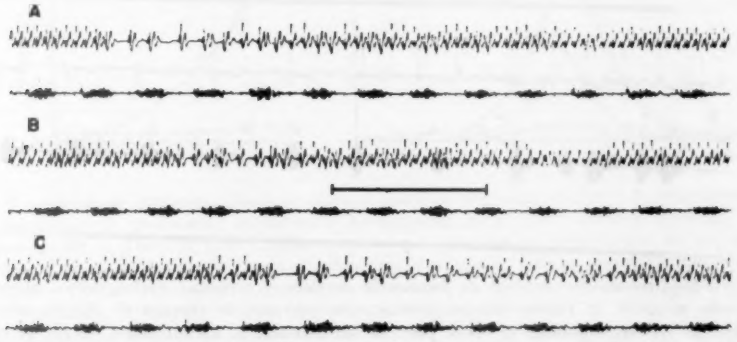

Fig. 1. — *Registros que muestran la diferencia de latencia al inyectar 50 microgramos de KCN por distintas vías. A. Aurícula izquierda. B. Tronco braquiocefálico. C. Aurícula derecha. Registro superior, frecuencia cardíaca. Registro inferior, actividad diafragmática. El principio del registro señala el momento de la inyección. Calibración de tiempo, 5 segundos.*

En ocasiones estas dosis tuvieron poco efecto sobre la frecuencia cardíaca y marcado efecto respiratorio (Fig. 2).

Para una determinada ventilación pulmonar la estimulación del cabo cen-

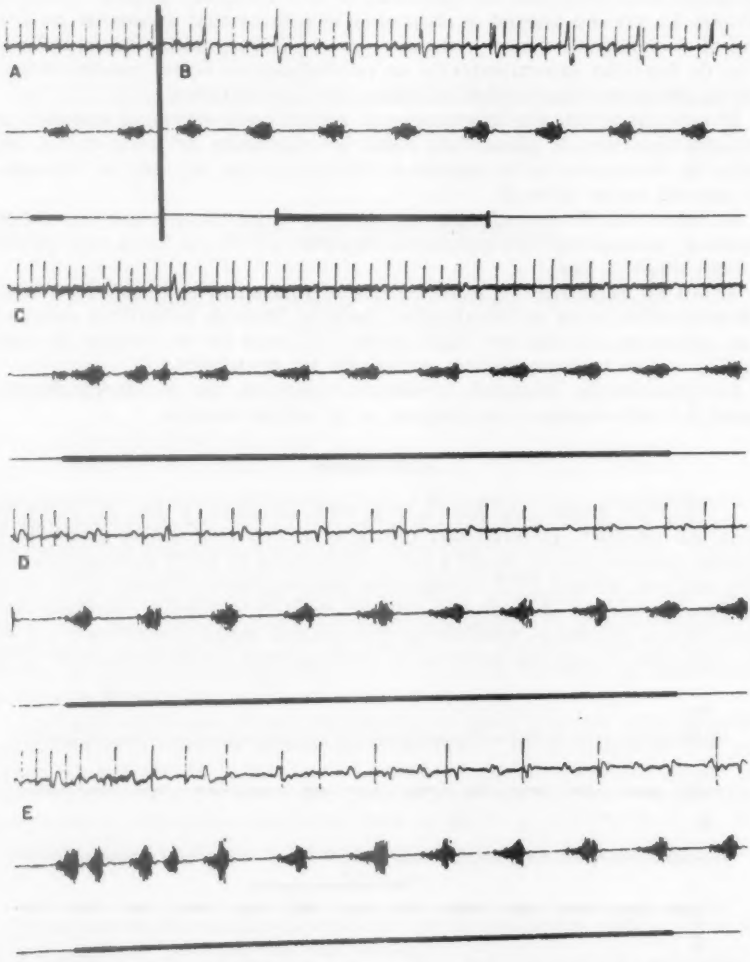

FIG. 2.—*Registro de los cambios de frecuencia cardíaca y actividad diafragmática durante la inyección de KCN. A. Valores basales previos a la inyección de cianuro. B. Efectos obtenidos al inyectar 100 microgramos de KCN por vía intravenosa. C. Estimulación de los depresores a 16/s. D. Estimulación de los depresores a la misma frecuencia 15 segundos después de la inyección de 100 microgramos de KCN. E. Lo mismo que en D, pero después de 200 microgramos de KCN. Registro superior, frecuencia cardíaca. Registro medio, actividad diafragmática. Señal inferior, artefacto del estímulo. Calibración de tiempo, 5 segundos.*

tral del nervio aórtico produjo un alargamiento del ciclo cardíaco que dependió de la frecuencia de estimulación (Fig. 3 B).

II. — *Efectos obtenidos al estimular los depresores después de la inyección de KCN.* Al estimular uno o ambos depresores 5 a 10 segundos después de haber inyectado 100 microgramos de KCN por vía intravenosa, se observó una bradicardia intensa, mucho mayor que la que correspondía a la suma algebraica de los efectos obtenidos por la estimulación aislada de los depresores y los de la inyección de cianuro (Figs. 2 a 5). Para una determinada frecuencia de estimulación de los depresores, la magnitud y velocidad con que se estableció este efecto fué función de la dosis de cianuro empleada (Figs. 2 y 3). Análogamente, para una dosis fija de cianuro el aumento dependió de la frecuencia de estimulación (Fig. 4). Este efecto, al que llamaremos potenciación, se apreció tanto con la estimulación unilateral como con la simultánea de los depresores, con ambos vagos íntegros o con uno de ellos seccionado (Fig. 6). En esas circunstancias se observó que el efecto de la estimulación simultánea de ambos depresores fué mucho mayor que la suma de los efectos de las estimulaciones unilaterales (Fig. 6). Esta potenciación desapareció al seccionar ambos vagos (Fig. 6). Cuando se inyectó cianuro una vez establecida la bradicardia debida a la estimulación de los depresores, se observó un aumento adicional del efecto cuya magnitud y duración dependieron de la dosis empleada.

La potenciación producida por una determinada dosis de cianuro dependió importantemente de la vía utilizada. Esta fué mayor cuando la inyección se efectuó por vía intravenosa, en aurícula o en la arteria pulmonar que cuando se inyectó en la aurícula izquierda o en el tronco braquiocefálico (Figs. 7 y 8).

La potenciación obtenida al inyectar cianuro del lado derecho de la circulación dependió del momento en que se estimuló el depresor. Así, para inyec-

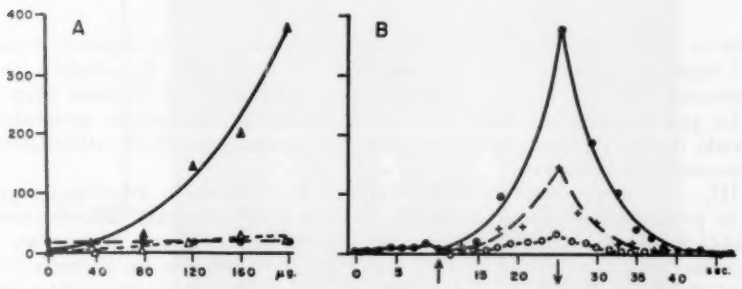

FIG. 3. — *Efecto de diferentes dosis de cianuro sobre la respuesta refleja a la estimulación de los depresores. A. Ordenadas, incrementos porcentuales en el ciclo cardíaco. Abscisas, microgramos de KCN. Círculos llenos, valor máximo que produce la estimulación de los dos depresores a 16/s (unidos por la línea discontinua). Triángulos blancos, alargamientos máximos producidos por las inyecciones intravenosas de cianuro a las dosis indicadas (unidos por la línea punteada). Triángulos llenos, incrementos máximos obtenidos al estimular los depresores 15 segundos después de la inyección de las dosis correspondientes de cianuro (unidos por la línea sólida). B. Cursos temporales del efecto obtenido por la estimulación de los dos depresores 15 segundos después de la inyección de diferentes dosis de cianuro. Círculos blancos, 80 microgramos. Cruces, 120 microgramos y círculos llenos 200 microgramos de KCN. Las flechas indican el tiempo de aplicación del estímulo.*

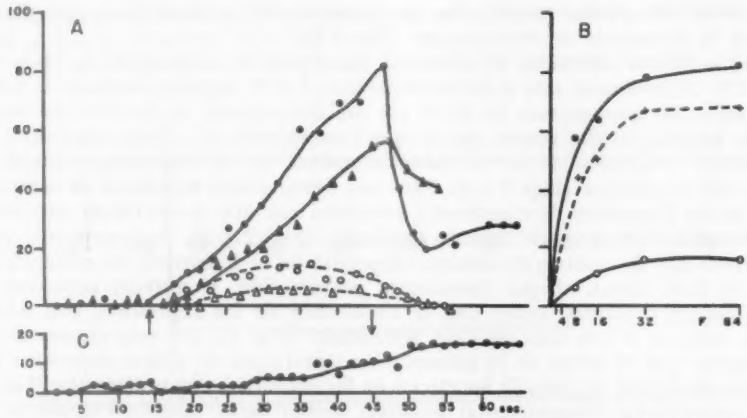

FIG. 4. — *Efectos de distintas frecuencias de estimulación de los depresores después de la inyección de 200 microgramos de KCN. A. Curso temporal de los efectos obtenidos por la estimulación aislada del depresor izquierdo (línea discontinua, símbolos blancos) y 15 segundos después de la inyección intravenosa de 200 microgramos de KCN (línea continua, símbolos llenos). Triángulos, a una frecuencia de estimulación de 8/s. Círculos, a 32/s. Las flechas indican el tiempo de aplicación del estímulo. B. Curva que relaciona los máximos de las respuestas obtenidas al estimular el depresor izquierdo a distintas frecuencias. Círculos blancos, curva obtenida al estimular el depresor izquierdo sólo. Círculos llenos, curva obtenida estimulando el depresor izquierdo 15 segundos después de la inyección de 200 microgramos de KCN. Si a la curva de círculos llenos se le restan los incrementos obtenidos por la inyección de cianuro se obtiene la curva discontinua. C. Curso temporal de los efectos producidos por la inyección intravenosa de 200 microgramos de KCN.*

ciones en la aurícula derecha ésta fué máxima al estimular el depresor entre los 2 a 3 segundos subsiguientes a la inyección (Fig. 7 C y E). En cambio, cuando se estimuló entre los 11 y 15 segundos, la potenciación fué mínima (Fig. 7 D).

La potenciación obtenida por las inyecciones intraarteriales generalmente fué nula o mínima, independientemente del tiempo cuando se estimularon los depresores (Fig. 7 A y B).

III. — *Pulmón aislado circulatoriamente.* Los resultados anteriores sugerían que la potenciación producida por la inyección de pequeñas dosis de cianuro se debía fundamentalmente a una contribución del territorio pulmonar. Para comprobar esta hipótesis se decidió aislar circulatoriamente un pulmón y estudiar el efecto del KCN inyectado en el circuito aislado. Para ello se hizo que la sangre arterial hipóxica de un donador entrase por una de las ramas principales de la arteria pulmonar, saliendo por las venas pulmonares correspondientes, para regresar por vía venosa al donador. Para asegurarse del aislamiento circulatorio de esa porción pulmonar, se inyectó tinta china en el circuito al final de cada experimento.

En tres experimentos satisfactorios la inyección de 200 a 500 microgramos de KCN en el pulmón aislado aumentó el efecto de la estimulación del depresor (Fig. 8 C). En ocasiones, con dosis menores (100 a 200 microgramos) aunque no hubo un aumento adicional importante del ciclo cardíaco, la latencia se acortó significativamente de una manera análoga a como se ilustra en la

Figura 9 B. Estos aumentos de efecto o disminuciones de latencia fueron siempre reversibles, aunque el tiempo en que se recuperaron los valores controles fué mayor (3 a 5 minutos) que cuando la misma dosis de cianuro se inyectó en el animal receptor por vía intravenosa (Fig. 7 D). Esto puede explicarse por el edema pulmonar y flujo reducido que existían en el pulmón aislado.

Las dosis de cianuro utilizadas no produjeron por sí mismas cambios de

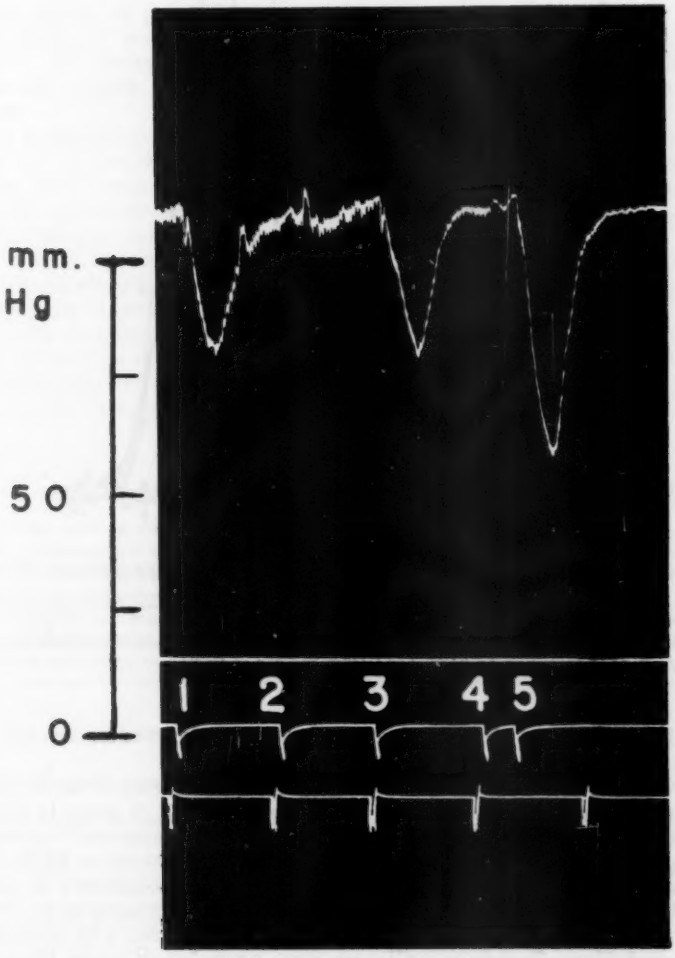

FIG. 5. — *Registro quimográfico de los cambios en la presión arterial. 1 y 3 durante la estimulación de los dos depresores a 16/s. 2. Efecto de la inyección intravenosa de 100 microgramos de KCN. 4 y 5. Inyección de 100 microgramos de KCN y estimulación de los dos depresores 15 segundos después. Señal de tiempo, un minuto.*

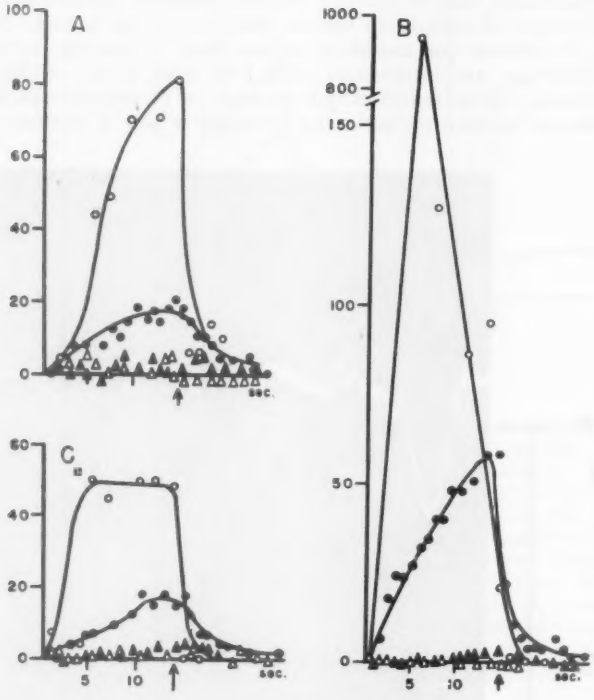

FIG. 6. — *Curso temporal de los efectos producidos al estimular los depresores 15 segundos después de la inyección intravenosa de 100 microgramos de KCN. A. Estimulación del depresor izquierdo. B. Del depresor derecho. C. De ambos depresores simultáneamente. Los círculos son puntos obtenidos en el animal con vagotomía izquierda. Los triángulos, en animal con vagotomía unilateral. Símbolos llenos, valores control. Símbolos claros, efectos obtenidos al estimular después de la inyección de KCN. Las flechas indican el tiempo de aplicación del estímulo.*

frecuencia cardíaca, ni de actividad respiratoria o de presión arterial en el receptor.

IV. — *Aplicación local de KCN.* Al estimular el depresor 10 a 15 segundos después de haber colocado papel filtro impregnado en KCN sobre la superficie pulmonar, se observó una potenciación muy intensa. Su magnitud dependió del área de papel en contacto con el pulmón, y de la concentración de KCN (Fig. 9). La potenciación disminuyó con el tiempo y desapareció totalmente al quitar el papel filtro, recuperándose los valores controles. Igual potenciación se obtuvo al inyectar por vía intravenosa una dosis de cianuro semejante a la total que poseía el papel filtro. Cuando se utilizaron áreas pequeñas de papel filtro (entre 3 y 5 cm^2) se tuvo un acortamiento muy importante de la latencia de la bradicardia sin que aumentase importantemente el ciclo cardíaco (Fig. 9 B). Estos efectos potenciadores también se presentaron al realizar la maniobra con las venas y arterias pulmonares ocluídas temporalmente en el lóbulo correspon-

diente. También se presentaron al colocar el papel filtro sobre el pulmón aislado circulatoriamente.

Al utilizar áreas grandes y soluciones más concentradas (10 mg/cm^3) se observó que la aplicación exclusiva del papel filtro produjo una bradicardia que alcanzó valores hasta de un 60 a 70 por ciento, elevación de la presión arterial y actividad respiratoria intensa. En esas condiciones también se produjo potenciación al estimular el depresor.

Al colocar el papel filtro en otras zonas de la cavidad torácica (corazón, pleura parietal), no se observó potenciación o ésta fué muy pequeña.

V. — *Vía aferente y eferente.* De acuerdo con el tipo de potenciación producida fué posible agrupar a los animales de experimentación en la forma siguiente:

a) Animales con potenciación marcada. La potenciación producida al estimular los nervios depresores a una frecuencia óptima (32/s), después de la inyección intravenosa de cianuro (50 a 100 microgramos) alcanzó valores muy elevados, produciendo en ocasiones hasta paro cardíaco (potenciaciones hasta de un 1000 por ciento). (Véase figuras 8 y 7 C).

En estos animales la inyección aislada de las mismas dosis de KCN produjo una bradicardia intensa, de latencia corta (3 a 10 segundos) (Fig. 1) y una elevación de la presión arterial.

Tanto la potenciación como la bradicardia producida por el KCN persistieron después de una sección medular a nivel de C_5 ó C_6. También se obtuvieron al extirpar las cadenas simpáticas torácicas. En cambio, desaparecieron totalmente con la vagotomía bilateral (Fig. 6) o después de atropinizar al animal.

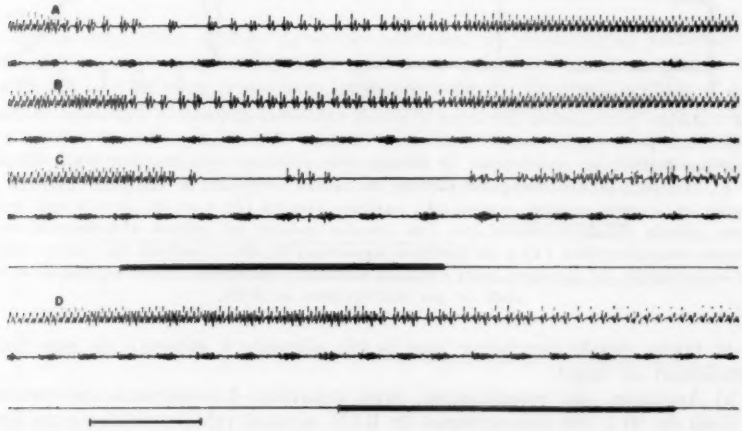

FIG. 7. — *Efectos de la estimulación de los dos depresores a 32/s después de la inyección de 50 microgramos de KCN por distintas vías. A. 5 segundos después de la inyección en aurícula izquierda. C. 5 segundos después de la inyección en aurícula derecha. D. 15 segundos después de la inyección en la aurícula derecha. Registro superior, frecuencia cardíaca. Registro inferior actividad diafragmática. El artefacto señala el tiempo de estimulación de los depresores (el de C es el mismo que para A y B). Calibración de tiempo, 5 segundos. El principio de los registros señala el momento de la inyección.*

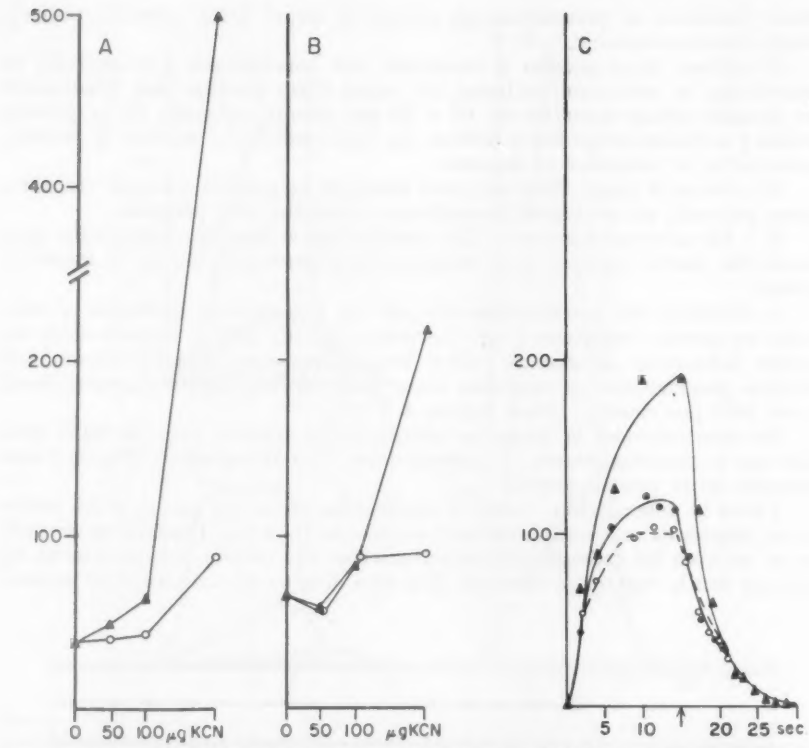

FIG. 8.—*Acción potenciadora del cianuro en los territorios sistémico y pulmonar. Ordenadas, alargamientos porcentuales máximos del ciclo cardíaco al estimular ambos depresores a 32/s, 5 segundos después de la inyección de cianuro por distintas vías. Abscisas, dosis de cianuro (A y B), tiempo (C). Los triángulos indican los efectos obtenidos al estimular después de la inyección en la vena yugular externa (A), aurícula derecha (B) y en el circuito que irriga al pulmón aislado circulatoriamente (C). Los círculos indican los valores obtenidos al inyectar en tronco braquiocefálico (A) y en aurícula izquierda (B). En C indican los valores controles de la estimulación del depresor antes (círculos blancos) y después (círculos negros) de la inyección de 500 microgramos de KCN.*

Por lo tanto, puede concluirse que la vía aferente y eferente de este tipo de potenciación es vagal.

b) Animales con potenciación muy reducida. La potenciación producida por dosis de 50 a 100 microgramos de KCN alcanzó valores máximos de un 100 a 200 por ciento. La inyección aislada de estas dosis produjo una bradicardia pequeña de latencia muy grande (15 a 30 segundos) (Fig. 4). Estas dosis produjeron una caída de la presión arterial. En un experimento satisfactorio se observó que los efectos sobre frecuencia cardíaca persistieron después de la atropinización, desapareciendo al extirpar las cadenas simpáticas torácicas o al seccionar ambos vagos. Por lo tanto, puede concluirse que este tipo de potenciación se puede deber fundamentalmente a una inhibición del tono simpático.

c) Animales con potenciación intermedia. La potenciación producida por dosis de cianuro semejantes a las anteriormente mencionadas alcanzó valores de un 400 a 500 por ciento. La inyección aislada de esas dosis produjo una pequeña bradicardia de latencia muy grande (Fig. 2), y una elevación de la presión arterial seguida de una caída. Posiblemente esta potenciación sea de un tipo intermedio entre los dos anteriormente mencionados.

Discusión

Hasta la fecha todos los trabajos relacionados con la actividad refleja quimio- y barorreceptora se basan fundamentalmente en el estudio de cambios mesurables, que nosotros llamaremos umbrales, de frecuencia cardíaca, actividad respiratoria, y presión arterial (Véase [9, 14, 19]). Es posible sin embargo, que la activación de estos receptores produzca estados de actividad subliminal que sólo podrán ser detectados con determinados métodos. El que nos pareció más adecuado fué el del estudio de la interacción de actividades reflejas que afecten a los mismos centros ([7]).

Schmidt y Comroe ([19]) y Álvarez-Buylla ([2]) sugieren, teniendo en cuenta que el cianuro produce bradicardia refleja en el animal anestesiado y que éste no activa sino deprime a los barorreceptores cardioaórticos y senocarotídeos, que los quimiorreceptores activan el centro cardioinhibidor.

Por otro lado, es bien sabido que la estimulación eléctrica del nervio aórtico activa también ese centro ([14, 16]). Si bien es cierto que la aferentación obtenida al estimularlo no proviene únicamente de fibras barosensibles, sino además de fibras de origen quimiorreceptor ([1]), constituye siempre una aferentación constante de características definidas lo que permite hacer estudios incluso cuantitativos.

Cuando concurren ambos tipos de actividad la bradicardia obtenida es mucho mayor que la que corresponde a la suma algebraica de la respuesta que produce cada una de estas maniobras individualmente consideradas (Figs. 2 a 7). Estos resultados demuestran que tanto las señales baroaferentes como las quimioaferentes concurren en algún punto dentro del mismo sistema y que al activarse independientemente producen un cierto grado de actividad subliminal que alcanza el umbral para descargar cuando su activación es simultánea.

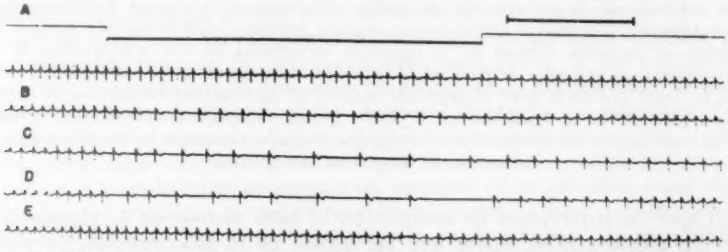

Fig. 9. — *Cambios de frecuencia cardíaca obtenidos al estimular los dos nervios depresores a 32/s. 15 segundos después de la aplicación sobre el pulmón de diferentes áreas de papel filtro impregnado en una solución de 1 mg/cm³ de KCN. A. Control. B. Después de aplicada un área de 4 cm². C. Después de aplicar un área de 9 cm². D. Después de un área de 13 cm². E. Estimulación de los depresores 3 minutos después de haber quitado el papel filtro de área grande. Señal de calibración, 5 segundos. La línea superior indica el tiempo de aplicación del estímulo.*

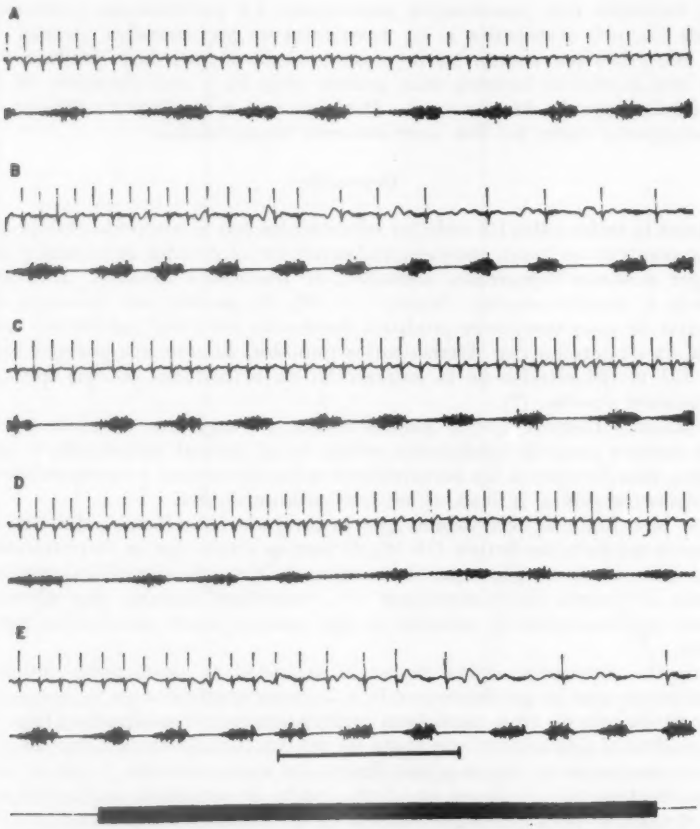

FIG. 10.—*Efectos de la estimulación de ambos depresores a 32/s sobre frecuencia cardiaca (registro superior) y actividad diafragmática (registro inferior). A. Estimulación control. B. Estimulación 10 segundos después de la inyección intravenosa de 100 microgramos de KCN. C. Estimulación 10 segundos después de la inyección intravenosa de 50 microgramos de adrenalina. D. Igual que en B pero 10 segundos después de la inyección intravenosa de 50 microgramos de adrenalina. E. Igual que en B pero 2 minutos después de la inyección intravenosa de 50 microgramos de adrenalina. La señal inferior indica el tiempo de aplicación del estímulo. Calibración de tiempo, 5 segundos.*

El que las inyecciones de cianuro en el lado venoso de la circulación tuviesen un efecto mucho mayor que las hechas en el lado arterial, ya permitía suponer que este efecto se debía a una contribución del territorio pulmonar. Los experimentos del pulmón aislado circulatoriamente y los de aplicación local de KCN apoyan este punto de vista (Figs. 7, 8 y 9). En algunas ocasiones se observó que las inyecciones realizadas en la aurícula izquierda poseían un efecto potenciador (Fig. 7). Esto se debe probablemente a que se estimulen los aferentes pulmonares al llegar la sangre con cianuro por vía coronaria.

Con los hechos existentes hasta la fecha no es posible saber qué tipos de terminaciones pulmonares son las que estimula el cianuro. Existen receptores pulmonares que son estimulados por la veratridina (8), y de la misma forma podrían ser estimulados por el cianuro. Esto es poco probable, pues al estimular los depresores después de haber inyectado 100 microgramos de veratridina por vía intravenosa, no se observó potenciación. Para aclarar el problema se necesita más evidencia experimental.

Como pueden encontrarse dosis de cianuro que careciendo de efectos umbrales sobre frecuencia cardíaca y presión arterial producen una potenciación muy importante (Fips. 2, 3 y 5), puede concluirse que sus efectos son subliminales y que sólo se manifiestan al concurrir con otro tipo de actividad refleja. Esta actividad subliminal se presenta con una latencia breve (2 a 3 segundos) y es de corta duración (Fig. 9). Esta interpretación explica satisfactoriamente aquellos experimentos hechos con el pulmón aislado circulatoriamente en los cuales ni el cianuro, ni la sangre hipóxica producen cambios umbrales de frecuencia cardíaca y presión arterial en el animal receptor (5, 6, 9).

Posible papel de los quimiorreceptores. De los resultados expuestos puede concluirse que existe una diferencia importante entre los efectos obtenidos por la estimulación de los quimiorreceptores y quimiorreflejos de diferentes zonas. Así, la activación de los quimiorreceptores cardioaórticos y senocarotídeos produce una bradicardia intensa, acompañada de un aumento de la actividad respiratoria y una elevación de la presión arterial (3, 14, 15). Sin embargo, los efectos subliminales de estos receptores son reducidos (Figs. 7 y 8).

Por otro lado, la activación de los receptores pulmonares produce potenciaciones muy importantes cuando ésta coincide con la estimulación del depresor, careciendo en cambio prácticamente de efectos umbrales cuando únicamente son estimulados por el KCN. Por lo tanto, el posible papel de estos últimos parece estar confinado en producir un cierto estado excitatorio central, logrando así que señales aferentes de otro tipo produzcan una respuesta mayor. Es decir, actuando como un "bias" en principio semejante al descrito para el sistema gamma (10).

Las dosis de cianuro necesarias para producir potenciación cuando se inyectan en el lado venoso, son semejantes a las que estimulan óptimamente a los quimiorreceptores senocarotídeos (3, 25). Además, durante la hipoxia o la asfixia se produce una descarga intensa de estos últimos quimiorreceptores (6). Es posible por lo tanto, que los receptores pulmonares sean activados también durante la asfixia o la hipoxia. De hecho esta interpretación es la que explica que la hipoxia o la hipoventilación potencien los efectos de la estimulación de los barorreceptores (18) desapareciendo estos efectos al denervar los pulmones (13).

Vía aferente y eferente. Los resultados descritos en la sección V indican que la potenciación se debe a señales que llegan a los centros por vía vagal. Las potenciaciones intensas se deben a un aumento de la actividad vagal eferente. En cambio las pequeñas se deben fundamentalmente a una disminución de la actividad simpática. Con el material experimental existente no es posible analizar cuáles son las condiciones que determinan que se active uno u otro tipo de vía eferente. En animales ligeramente anestesiados las respuestas potenciadoras son intensas y disminuyen al profundizar la anestesia. Asimismo, la potenciación producida aumenta al disminuir la ventilación del animal o la concentración de oxígeno en la mezcla gaseosa que respira (18). De una manera análoga la potenciación aumenta, dentro de ciertos límites, al disminuir la

concentración de glucosa en sangre (12). Es posible por lo tanto que la suma integral de estos factores, y de muchos otros aún no analizados, sea la que determine en un momento dado el tipo de vía eferente que se active. Para aclarar el problema es necesaria más evidencia experimental.

Papel de la adrenalina. Pequeñas dosis de adrenalina potencian la respuesta obtenida por la estimulación del depresor (18, 20). Podría ser, por lo tanto, que al activarse los quimiorreflejos hubiese una liberación concomitante de adrenalina, siendo ésta la que potenciase la respuesta a la estimulación del depresor. Sin embargo, dado que pueden encontrarse dosis de cianuro que prácticamente no modifican la presión arterial (Fig. 5) ni la frecuencia cardíaca (Fig. 2) y que producen potenciación, y que, además, durante la estimulación del depresor se inhibe la secreción de adrenalina (21, 22), puede considerarse que la cantidad liberada en esas condiciones es mínima. Rudomín, Erlij y Eberstadt (18) señalan que con dosis de 2.5 microgramos, que producen una elevación de la presión arterial de 30 mm de Hg, la potenciación obtenida alcanza hasta un 10 por ciento como máximo. Con dosis elevadas de adrenalina (50 a 100 microgramos) se inhibe la respuesta obtenida por la estimulación de los depresores (18) y también la acción potenciadora del cianuro (Fig. 10). Por lo tanto puede concluirse que, dentro de las condiciones en que se realizaron estos experimentos, la secreción de adrenalina no influye importantemente.

Estimulación del cabo periférico del vago. La estimulación del cabo periférico de cualquiera de los dos vagos no se vió potenciada después de las inyecciones de cianuro. Incluso en algunas ocasiones se obtuvo disminución del efecto.

Resumen

Se realizaron 56 experimentos en conejos anestesiados con pentobarbital sódico (25 a 35 mg/kg I. V.). Los nervios depresores aórticos se disecaron en la región cervical. Se tomaron registros eléctricos de la frecuencia cardíaca y de la actividad diafragmática, así como de la presión arterial. El animal se mantuvo con respiración artificial durante el experimento.

La inyección intravenosa de pequeñas dosis de KCN (50 a 100 microgramos) potencia la bradicardia obtenida por la estimulación del depresor (Fig. 2). Estos efectos dependen de la dosis de KCN y de la frecuencia de estimulación del depresor (Figs. 2, 3, 4 y 6). Las dosis de cianuro empleadas presentan pocos efectos umbrales sobre frecuencia cardíaca (Figs. 2, 3, 4) y presión arterial (Fig. 5).

La potenciación producida es mucho mayor cuando las inyecciones se realizan por vía intravenosa, aurícula derecha o arteria pulmonar que al inyectar en aurícula izquierda o en tronco braquiocefálico (Figs. 7 y 8). También se observa esta potenciación al inyectar cianuro en el circuito que irriga al pulmón aislado circulatoriamente (Fig. 8 C), o al estimular el depresor después de la aplicación local sobre el pulmón de papel filtro impregnado en solución de KCN (Fig. 9).

De los resultados anteriores se concluye:

1. Inyecciones intravenosas de pequeñas dosis de KCN potencian la actividad del centro cardioinhibidor, fundamentalmente por la activación de receptores pulmonares cuyas señales llegan a los centros por vía vagal.

2. Las descargas de estas fibras son de efectos reflejos subliminales, y el estado excitatorio que producen en el centro cardioinhibidor se pone de manifiesto cuando se activa simultáneamente el nervio depresor.

3. A diferencia de los receptores pulmonares la activación de los quimiorreceptores cardioaórticos y senocarotídeos produce efectos umbrales en su mayor parte.

Summary

The purpose of this paper was to study the influence of the chemoreceptors upon the cardioinhibitory centers. The bradycardia produced by stimulation of the aortic nerve was taken as an index of the activity of these centers. The circulatory chemoreceptors were activated by KCN injections.

56 experiments were performed in anesthetized rabbits (25 to 35 mg per kg, sodium pentobarbital). The depressor nerves were dissected in the cervical region. Cardiac frequency and electrical diaphragmatic activity were recorded. The animal was kept with artificial respiration.

The response obtained by depressor stimulation became potentiated when the stimulation was repeated after intravenous injections of 50 to 100 micrograms of KCN (Fig. 2). The effects were a function of the doses employed and of the frequency of stimulation (Figs. 2, 3, 4, 6). These doses have little effects upon cardiac frequency (Figs. 3, 3, 4) and arterial blood pressure (Fig. 5).

Intravenous, right atrium and pulmonary arterial injections had more effects than those made into the left atrium or brachiocephalic trunk (Figs. 7, 8). The potentiation also appeared by injecting cyanide into the circulation of the isolated lung (Fig. 8 C), or by local application to the lung of filter paper soaked in cyanide solution (Fig. 9).

It is concluded that the reflex activity of the cardioinhibitory centers is potentiated by intravenous injections of cyanide, which activates afferent vagal pulmonary receptors. These afferent discharges produce a reflex subliminal activity, which becomes noticeable by the coincident depressor nerve stimulation. Cardioaortic and carotid sinus chemoreceptor activation produces mainly threshold reflex effects.

Los autores agradecen a los Dres. P. Eberstadt, y D. Erlij la valiosa ayuda prestada durante este trabajo. Agradecen también al Dr. O. Krayer por su gentileza al obsequiar la veratridina utilizada y al Dr. A. Rosenblueth las valiosas críticas y correcciones hechas al manuscrito.

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INFLUENCIA DE LA HIPOXIA E HIPOVENTILACIÓN SOBRE LA SUMACIÓN TEMPORAL Y ESPACIAL DEL CENTRO CARDIOINHIBIDOR (*)

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En una publicación previa Rudomín y Deutsch (15, 16) comunicaron que la bradicardia refleja producida por la hipoxia varía según el grado de ventilación pulmonar. Estos cambios de frecuencia dependían de la actividad del centro cardioinhibidor.

En el presente trabajo se estudian las características de sumación espacial y temporal de este centro durante diferentes grados de ventilación. Su actividad se juzgó por los cambios reflejos de frecuencia cardíaca producidos por la estimulación eléctrica de los nervios aórticos en el conejo (13, 14).

MÉTODO

Se emplearon 30 conejos anestesiados con pentobarbital sódico (25 a 35 mg/kg por vía intravenosa). Se abrió el cuello por la línea media y una vez disecada y canulada la tráquea se prepararon ambos depresores de acuerdo con la técnica descrita por Álvarez-Buylla (1).

Para registrar la frecuencia cardíaca se colocó un par de electrodos en la región precordial del animal (o en el corazón cuando se abría el tórax), y para el registro de la actividad eléctrica del diafragma otros dos en la inserción xifoidea de dicho músculo. Las señales eléctricas procedentes de estos electrodos se registraron en un electroencefalógrafo (Modelo III de Grass). La presión arterial se registró en el cabo central de una de las arterias femorales.

(*) Este trabajo fué realizado con la ayuda proporcionada por "Life Insurance Medical Research Fund".

Received for publication, April 5th, 1959.

Como estímulos se emplearon pulsos rectangulares de 1.5 mseg de duración, provenientes de un estimulador de Grass (Modelo S 4) y aislados de tierra por una unidad aisladora (S. I. U. de Grass). El cabo central de los depresores o el periférico del vago se colocó sobre electrodos bipolares de plata. Para evitar la desecación de los nervios y aislarlos del resto de los tejidos, se cubrieron en todo su trayecto con una capa de aceite mineral. La intensidad de los estímulos fué siempre 4 veces la que producía un efecto máximo al estimular el cabo central del depresor a 32/seg o a 5/seg el cabo periférico del vago, según el caso.

Todos los experimentos se realizaron en el animal con respiración artificial. Los cambios de frecuencia cardíaca se juzgaron por el alargamiento porcentual del ciclo cardíaco, con respecto a los valores basales. El resto de los detalles de método se indican en las secciones correspondientes de los resultados.

Resultados

I. *Influencia de la ventilación pulmonar*

A. *Volumen pulmonar variable.* — Para una determinada ventilación pulmonar, la estimulación del cabo central del nervio aórtico produce un alargamiento del ciclo cardíaco que depende de la frecuencia de estimulación (Fig. 1).

En la mayor parte de las observaciones, cada uno de los depresores estimulado aisladamente produjo un efecto semejante al del contralateral (Fig. 1). Al estimular ambos depresores durante hiperventilación, se obtuvo un efecto mayor que estimulándolos aisladamente, pero menor que la suma algebraica de sus efectos individuales (Fig. 1).

Al disminuir el volumen de ventilación pulmonar se observó un aumento del efecto obtenido al estimular los depresores (Fig. 2). Al regresar la ventilación a sus niveles previos, se recuperaron los valores iniciales.

Los incrementos máximos obtenidos al estimular los depresores durante distintos niveles de ventilación, dependieron de variaciones individuales y del grado de anestesia. Por ejemplo, en el experimento que ilustra la Figura 2 al disminuir el aire corriente de 100 a 40 cm^3 se obtuvieron incrementos hasta de un 100 por ciento. Los aumentos de presión arterial en esas condiciones no excedieron de 25 mm de Hg. En cambio en el experimento que ilustra la Figura 1 (A, B y C) hecho en un animal con un mayor grado de anestesia, los cambios porcentuales fueron menores, observándose que durante la hipoventilación los valores máximos obtenidos al estimular los depresores por separado, tendieron a ser semejantes a los obtenidos al estimular los dos depresores juntos. Frecuentemente, se observó también que durante hipoventilación los valores aumentaron para la estimulación bilateral, a semejanza de lo que se ilustra para la hipoxia en la Figura 1 E.

B. *Volumen pulmonar constante.* — Al mantener el volumen pulmonar constante y aproximadamente igual al que movilizaba el animal durante la respiración espontánea, el efecto obtenido por la estimulación unilateral o simultánea de los depresores fué hasta un 80 por ciento menor con oxígeno al 100 por ciento que cuando el animal respiró aire atmosférico (Figs. 1 E y 5) o bien cuando respiró oxígeno al 8 por ciento en nitrógeno.

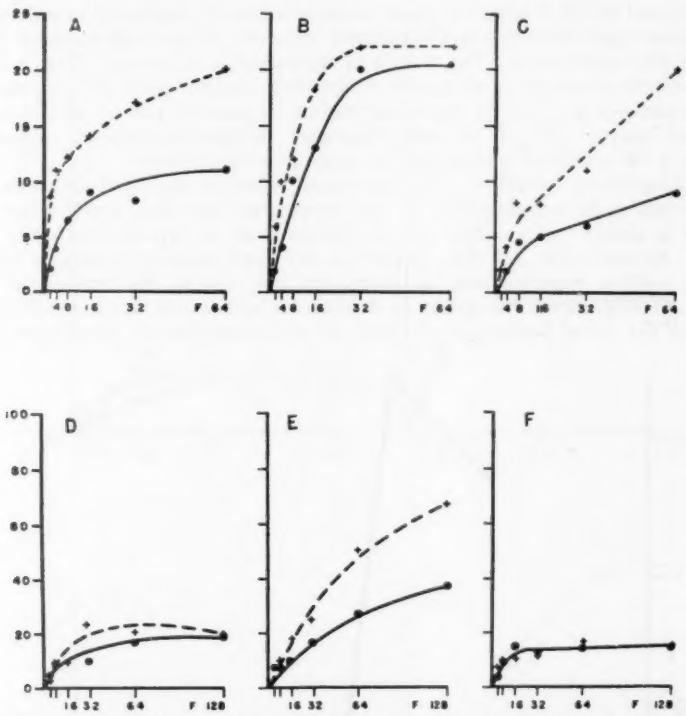

FIG. 1. — *Cambios producidos en la respuesta refleja a la estimulación del depresor durante cambios en el volumen de ventilación (A, B y C) y con volumen pulmonar fijo variando la concentración de oxígeno (D, E y F). Abscisas, frecuencia del estímulo. Ordenadas, alargamiento porcentual máximo del ciclo cardíaco. En A, B y C: línea continua, durante hiperventilación; línea discontinua, durante hipoventilación. En D, E y F: línea continua, durante ventilación con oxígeno 100 por ciento. Línea discontinua o cruces, durante aire atmosférico. A y D, estimulación del depresor izquierdo; C y F, del depresor derecho; B y E, estimulación simultánea de ambos depresores.*

II. *Efectos de la vagotomía*

A. *Vagotomía unilateral.* — La vagotomía unilateral podía disminuir, pero no suprimir, la respuesta refleja a la estimulación del depresor ipsilateral. El grado de disminución de la respuesta dependió de la ventilación o de la concentración de oxígeno en la mezcla que respiraba el animal. Al seccionar el vago durante la ventilación con oxígeno al 100 por ciento, con un volumen tal que no hubiera actividad del centro respiratorio, la respuesta a la estimulación del depresor ipsilateral cayó hasta un 50 por ciento de los valores previos a la sección (Fig. 3 D). Cuando el volumen fué tal que se tuvo actividad respiratoria y que ésta aumentó al seccionar el vago, la respuesta refleja ipsilateral prácticamente no cambió o fué incluso mayor que la control (Fig. 3 A). Ade-

más, en igual forma o como se señaló anteriormente, el efecto de la estimulación del depresor ipsilateral al vago seccionado aumentó al pasar de oxígeno 100 por ciento a aire atmosférico (Fig. 3 A) o al hipoventilar al animal (Fig. 5 A).

El efecto obtenido al estimular el depresor cambió poco con la vagotomía contralateral (Fig. 3 C). Al estimular ambos depresores juntos, el efecto obtenido fué mayor que el de cada depresor independientemente considerado (Fig. 3), y en ocasiones mayor que la suma de estos efectos.

B. *Vagotomía bilateral.* — La vagotomía bilateral suprimió casi totalmente la respuesta a la estimulación de los depresores. En esas condiciones no se observó la acción potenciadora de la hipoxia o de la hipoventilación.

III. *Estimulación del cabo periférico del vago durante hipoxia e hipoventilación.* — Estos experimentos se planearon con objeto de determinar si los hechos anteriormente observados se debían a efectos centrales o periféricos. Al estimular los cabos periféricos al final del experimento, en condiciones análo-

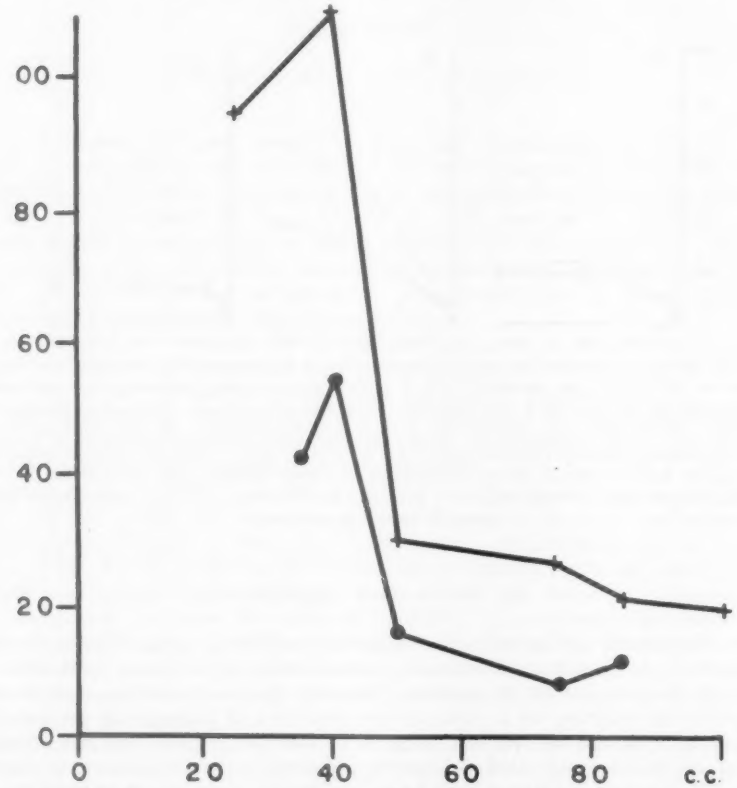

FIG. 2. — *Cambios producidos en la respuesta refleja a la estimulación del depresor durante variaciones en la ventilación pulmonar. Abscisas: volumen del aire corriente en cm³ (frecuencia respiratoria 24/min.). Ordenadas: alargamiento porcentual máximo del ciclo cardíaco. Círculos, para una frecuencia de estimulación de 40/seg. Cruces, para una frecuencia de 60/seg.*

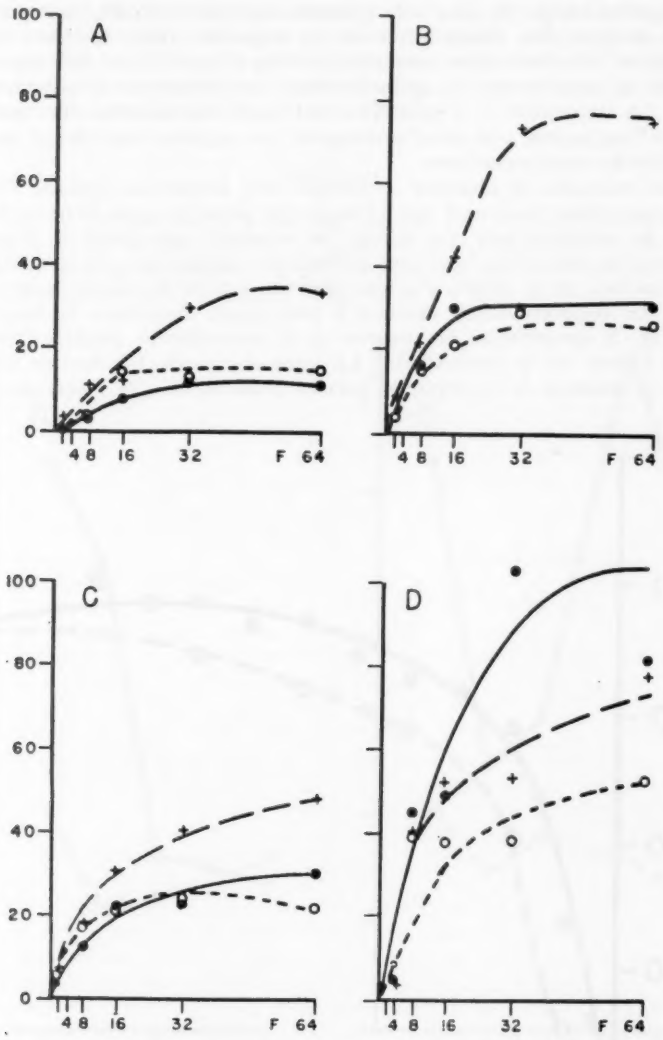

FIG. 3.—*Efectos obtenidos por la estimulación del depresor con vagotomía unilateral izquierda y volumen de ventilación constante. A y D, estimulación del depresor izquierdo; B, estimulación de los dos depresores simultáneamente; C, estimulación del depresor derecho. Línea continua, control durante ventilación con oxígeno 100 por ciento. Línea punteada, estimulación después de haber seccionado el vago izquierdo. Línea discontinua, ventilando con aire atmosférico. En A, B y C, ventilando con un volumen que determina actividad del centro respiratorio; en D, sin dicha actividad. Abscisas: frecuencia de estimulación. Ordenadas: alargamiento porcentual del ciclo.*

gas a aquellas en que se obtuvo la potenciación del efecto de los depresores, se observó siempre una disminución de la respuesta (Fig. 4). Estos controles se repitieron en condiciones más comparables y no al final del experimento. Para ello se estimuló en un mismo animal sucesivamente el cabo central de uno de los depresores y el periférico del vago contralateral. En esta forma pudieron compararse casi simultáneamente las acciones centrales y periféricas de las diversas manipulaciones.

Para estimular el depresor se escogió una frecuencia óptima (50/seg) y para el vago una frecuencia tal (5/seg) que producía una bradicardia semejante a la originada por vía refleja. Se encontró que tanto la hipoventilación como la ventilación con aire atmosférico aumentaron la actividad refleja. En cambio, en la periférica, sólo tuvieron acción en condiciones extremas (Fig. 5). La hipoventilación extrema o prolongada disminuyó la respuesta refleja (Fig. 2) persistiendo el aumento a la estimulación periférica del vago.

IV. *Efectos de la adrenalina.* — La estimulación de los nervios depresores durante el máximo de la respuesta presora consecutiva a la inyección de adre-

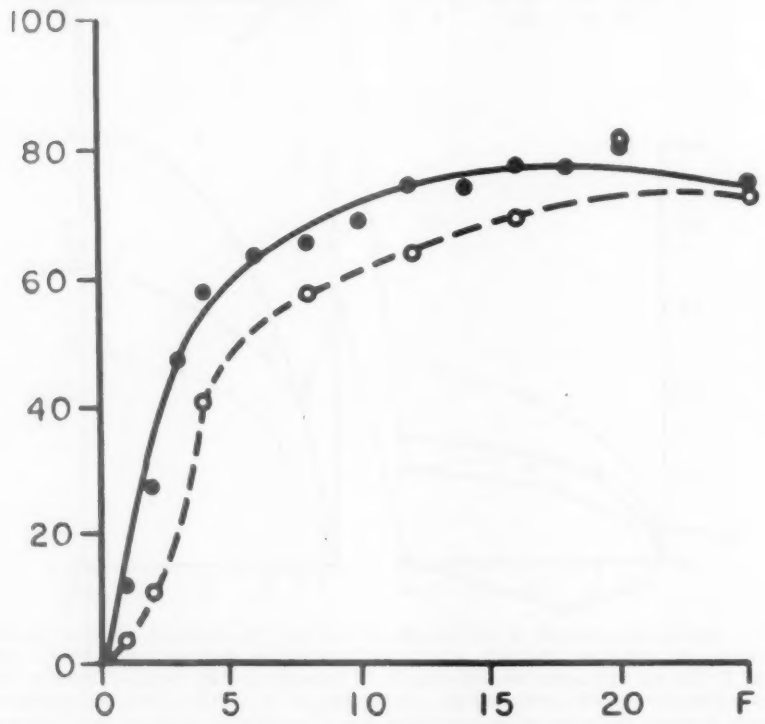

FIG. 4. — *Efectos de la estimulación durante hipoventilación del cabo periférico del vago. Curva continua control. Curva discontinua, durante hipoventilación. Abscisas, frecuencia de estimulación. Ordenadas, por ciento de alargamiento del ciclo cardiaco.*

nalina permitió observar dos tipos de respuesta (Fig. 6). Con dosis pequeñas (2.5 a 10 microgramos) se observó aumento del efecto reflejo. Este aumento alcanzó valores hasta de un 75 por ciento sobre los de control. Con dosis mayores, la respuesta disminuyó notablemente (Fig. 6) a pesar que los incrementos de la presión arterial fueron aún más elevados.

Discusión

Efectos de la ventilación. — La disminución del volumen de ventilación pulmonar produce un aumento de la respuesta refleja obtenida por la estimulación de los nervios depresores. La hiperventilación, por el contrario, produce una disminución de dicha respuesta (Figs. 1, 2, 3 y 5).

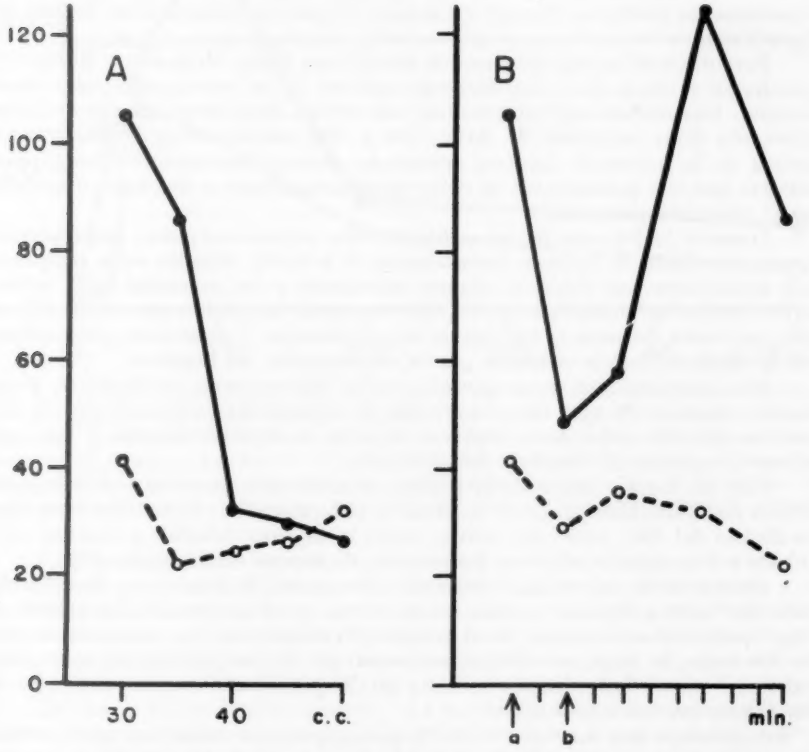

Fig. 5. — *Efectos producidos sobre el ciclo cardíaco por la estimulación del cabo central del depresor derecho (línea continua) y la del cabo periférico del vago izquierdo (línea discontinua). A. Cambios producidos al variar la ventilación pulmonar. Abscisas, aire corriente en cm³. Ordenadas, alargamiento porcentual del ciclo cardíaco. B. Curso temporal del efecto producido al ventilar con oxígeno 100 por ciento (a) o con aire atmosférico (b) manteniendo fijo el volumen pulmonar (30 cm³). Abscisas, tiempo en minutos.*

Heymans, Bouckaert y Samaan (9) consideran que al hiperventilar, las descargas aumentadas de los presorreceptores pulmonares inhiben la actividad refleja del centro cardioinhibidor. Esta interpretación no explica satisfactoriamente nuestros resultados. En los experimentos en que se mantuvo el volumen pulmonar constante, y por lo tanto había una descarga constante también de los presorreceptores pulmonares se observó que la actividad refleja del centro cardioinhibidor era mayor cuando se ventilaba al animal con aire atmosférico o con oxígeno al 8 por ciento en nitrógeno que con oxígeno al 100 por ciento (Figs. 1 E y 5).

Varios autores (25, 26) encuentran que la asfixia o hipercapnia aumentan la excitabilidad refleja del centro cardioinhibidor. Esa potenciación puede deberse a un efecto directo del exceso de CO_2 o a la falta de oxígeno sobre los centros (18) o bien a un efecto indirecto que estos agentes puedan producir a través de cambios en la actividad quimiorreceptora, como lo sugieren los resultados de Gellhorn, Cortell y Carlson (7) para la estimulación directa del hipotálamo.

Para discernir acerca del papel de este último factor, Rudomín y Rubio (17) estudiaron el efecto de la estimulación selectiva de los quimiorreceptores circulatorios. Encontraron que al estimular los nervios depresores después de haber inyectado dosis pequeñas de KCN (50 a 100 microgramos) la disminución refleja de la frecuencia cardíaca aumentaba extraordinariamente. Concluyeron además que esta potenciación se debe fundamentalmente a descargas originadas en el territorio pulmonar.

Durante la hipoventilación o hipoxia los quimiorreceptores cardioaórticos y senocarotídeos se activan intensamente (6, 9, 10, 18). Además estos receptores son estimulados por dosis de cianuro semejantes a las necesarias para activar a los receptores pulmonares (2, 17). Por lo tanto, es posible que estos últimos sean activados durante la hipoxia o hipoventilación y produzcan potenciación de la respuesta refleja obtenida por la estimulación del depresor.

Esta interpretación se ve apoyada por las observaciones de Heymans, Bouckaert y Samaan (9) que encuentran que la bradicardia producida por la distensión del seno carotídeo disminuye durante la hiperventilación, y que este efecto desaparece al denervar los pulmones.

Con los datos actuales no es posible discernir si la potenciación refleja del centro cardioinhibidor durante la asfixia o la hipoventilación, se debe a un efecto directo del CO_2 sobre este centro, como lo sugieren Schmidt y Comroe (18), o bien a descargas de aferentes pulmonares de efectos subliminales (17).

Efectos de la vagotomía unilateral. — Heymans (8) señala que la estimulación del nervio depresor aórtico en el conejo produce bradicardia sólo si el vago ipsilateral está intacto. Reed y Scott (12) encuentran que al seccionar uno de los vagos la respuesta refleja producida por la compresión del seno carotídeo del mismo lado disminuye hasta un 50 por ciento con respecto a la de los valores previos a la sección.

Sin embargo, hay autores (11, 24, 27) que opinan que existe un cruce central de vías, ya que, independientemente de la integridad de uno de los vagos, observan efectos semejantes al estimular cualquiera de los barorreceptores carotídeos. La falta de acuerdo que existe entre los autores antes mencionados puede explicarse a la luz de los hechos de este trabajo. Ninguno de ellos correlaciona directamente los efectos obtenidos con las condiciones de ventilación bajo las cuales se realizaron las observaciones.

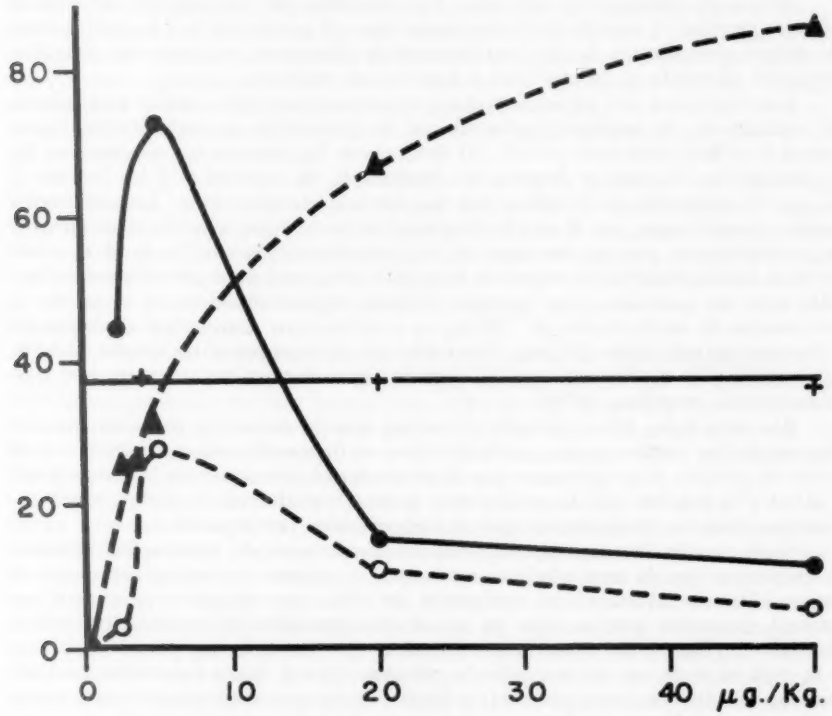

FIG. 6. — *Cambios producidos por diferentes dosis de adrenalina sobre la frecuencia cardíaca (círculos vacíos) y la presión arterial (triángulos). Las cruces indican los valores máximos obtenidos al estimular simultáneamente a los dos depresores a 32/seg. Los círculos llenos muestran la respuesta máxima al estimular los depresores a igual frecuencia, 15 segundos después de la inyección de diferentes dosis de adrenalina. Abscisas, dosis de adrenalina en microgramos. Ordenadas, incremento porcentual del ciclo cardíaco y de la presión arterial.*

La existencia mayor o menor de un cruce central depende de la ventilación del animal (véase sección II[3]). Éste aumenta al disminuir el aire corriente o la concentración de oxígeno de la mezcla gaseosa que respira (Fig. 3). Puede concluirse entonces, que la existencia funcional de esas vías cruzadas depende del grado de excitabilidad refleja del centro cardioinhibidor, a su vez determinado por factores reflejos (17) y directos (18).

Efectos de la vagotomía bilateral. — La vagotomía bilateral suprime notablemente el efecto reflejo obtenido por la estimulación de los depresores aórticos (27), y la potenciación obtenida en hipoxia o hipoventilación. Asimismo, en el animal atropinizado no se observa efecto potenciador alguno al estimular los depresores durante la hipoxia o la hipoventilación.

De lo anteriormente expuesto puede concluirse que la potenciación producida por la hipoxia e hipoventilación se debe fundamentalmente a un aumento de la actividad vagal y no a una disminución de la del simpático.

Sumación temporal y espacial. — La existencia de dos nervios depresores aórticos permite el estudio de la sumación espacial producida por la confluencia de señales procedentes de dos vías anatómicas diferentes, así como la sumación temporal obtenida al estimularlas a frecuencias variables.

Los resultados del presente trabajo muestran que, para ciertas condiciones de ventilación, la respuesta aumenta con la frecuencia de estimulación hasta adquirir valores máximos ([13, 14]). Al determinar las mismas curvas durante hipoventilación, hipoxia o después de inyecciones de cianuro ([17]) los valores a los que la respuesta se estabiliza son mucho más elevados (Fig. 1). Este hecho sugiere, desde luego, que el estado funcional de los centros, a su vez determinado importantemente por las descargas de los quimiorreceptores ([17]), es el que impone el límite máximo de sumación espacial y temporal para esas circunstancias. Más aún, en ocasiones, por ejemplo durante hiperventilación, la respuesta a frecuencias de estimulación de 128/seg es notablemente menor que la respuesta a frecuencias más bajas (64/seg). Sin embargo, al determinar las curvas durante hipoventilación se observa que el sistema sigue frecuencias mayores sin que disminuya la respuesta refleja.

Por otro lado, Álvarez-Buylla ([1]) señala que al estimular simultáneamente algunas de las ramas en que puede dividirse el depresor aórtico, se obtiene una caída de presión arterial mayor que al estimularlos por separado. Además Scott y Reed ([19]) señalan que la compresión manual simultánea de ambos senos carotídeos tiene un efecto mayor que al comprimirlos por separado.

Si se estudia la sumación espacial en condiciones de ventilación elevada, se encuentra que la estimulación simultánea de ambos depresores sobrepasa al efecto obtenido al estimular cualquiera de ellos por separado, pero que, en general, es menor que la suma de los efectos obtenidos al estimularlos individualmente (Fig. 1). De acuerdo con Creed *et al.* ([5]) este hecho puede atribuirse a la existencia de un cierto grado de oclusión central. Estos resultados no concuerdan con los señalados por Scott y Reed ([19]), ya que estos autores encuentran facilitación en la mayor parte de sus casos. Probablemente esta diferencia se debe a las condiciones de la preparación. En las condiciones que ellos citan haber encontrado facilitación (ventilando con oxígeno 100 por ciento) nosotros encontramos generalmente oclusión. En ocasiones puede verse un cierto grado de facilitación al comparar la postdescarga producida por la estimulación simultánea de ambos depresores con la producida por la estimulación unilateral. Cuando las estimulaciones se realizan durante ventilación con aire atmosférico (Fig. 1, D, E y F) o sobre todo después de haber inyectado cianuro ([17]), la respuesta a la estimulación simultánea de los depresores excede en mucho a la suma de los efectos máximos obtenidos por la estimulación individual de estos nervios.

Estos resultados indican que en estas condiciones, el aumento de las descargas quimiorreceptoras determina un crecimiento del área subliminal de cada uno de los depresores, disminuyendo el grado de oclusión central. El límite máximo que se puede alcanzar tanto por la sumación temporal o espacial depende fundamentalmente del grado de actividad funcional del centro cardioinhibidor. La actividad de este centro está condicionada en gran parte por las descargas quimioaferentes ([17]).

Efectos de la hipoxia e hipoventilación sobre la respuesta a la estimulación del cabo periférico del vago. — Heymans, Bouckaert y Samaan ([9]), y Szekeres ([21]) encuentran que la estimulación del cabo periférico del vago produce efectos mayores cuando el animal respira mezclas gaseosas con concentraciones elevadas

de CO_2. Podría pensarse que todos los resultados descritos anteriormente se debieran simplemente a un aumento del efecto periférico y no a una facilitación central. Los resultados descritos en la sección III indican que dentro de nuestras condiciones experimentales los efectos observados son mucho mayores cuando se considera la estimulación refleja que la periférica (Figs. 4 y 5). Por lo tanto la potenciación producida por estos agentes se debe en su mayor parte a un efecto central y no periférico.

Papel de la secreción de adrenalina. — Cannon y Hoskins (22), Bülbring, Burn y de Elio (3) encuentran que durante la hipoxia hay una liberación importante de adrenalina. Stella (20) señala que pequeña dosis de adrenalina inyectada en los centros aislados circulatoriamente, aumentan la respuesta refleja a la estimulación de los barorreceptores senocarotídeos (Fig. 6). Se plantea entonces el problema de hasta dónde la adrenalina determina los mecanismos de potenciación antes mencionados.

Los aumentos de presión arterial que se producen al hipoventilar, no excedieron en nuestros experimentos los 25 mm de Hg, por lo que la cantidad de adrenalina secretada en esas condiciones debe de ser pequeña. En efecto, con dosis de 2.5 microgramos que producen una elevación de la presión arterial de 30 mm de Hg aproximadamente, se obtuvo sólo un aumento del 8 por ciento en la respuesta refleja a la estimulación de los depresores (Fig. 6).

Por otro lado Tournade y Chabrol (22) y Tournade y Malméjac (23), obtienen una reducción de la secreción de adrenalina durante la estimulación de los nervios depresores aórticos y senocarotídeos. Además, pueden encontrarse dosis de cianuro tales que no modifican la presión arterial y que sin embargo tienen un efecto de potenciación marcado (17). Dosis elevadas de adrenalina disminuyen la respuesta producida por la estimulación de los depresores, e inhiben la potenciación producida por el cianuro (17). Por lo tanto, puede concluirse que, dentro de las condiciones en que se realizaron estos experimentos, la secreción de adrenalina no influyó importantemente sobre los efectos anteriormente discutidos.

Resumen

Se realizaron 30 experimentos en conejos anestesiados con pentobarbital sódico (25 a 35 mg/kg). Los nervios depresores aórticos se disecaron en la región cervical. Se tomaron registros eléctricos de la frecuencia cardíaca y de la actividad diafragmática así como la presión arterial. El animal se mantuvo con respiración artificial durante el experimento.

La respuesta refleja obtenida por la estimulación de los depresores disminuye al hiperventilar al animal. Este efecto es independiente del grado de distensión pulmonar, ya que también se presenta al hacer respirar al animal oxígeno 100 por ciento sin variar el volumen de ventilación.

Se concluye que la potenciación obtenida durante hipoventilación e hipoxia depende importantemente de la influencia que ejercen sobre el centro cardioinhibidor las señales procedentes de los quimiorreceptores.

La respuesta obtenida al estimular el depresor ipsilateral al vago seccionado depende de la ventilación. Durante la hipoventilación o después de cianuro, las respuestas obtenidas al estimular los depresores se ven significativamente potenciadas a pesar de la vagotomía unilateral. Como esta potenciación no se presenta después de la vagotomía bilateral o en el animal atropinizado, se concluye que este efecto se debe a un aumento de las descargas vagales.

El grado de sumación espacial y temporal se modifica importantemente al variar la ventilación del animal. Tanto la frecuencia que sigue el sistema, como el efecto obtenido, es mayor durante la hipoventilación e hipoxia que cuando se ventila con grandes volúmenes pulmonares u oxígeno 100 por ciento (Fig. 1). De una manera semejante, la oclusión obtenida al estimular los dos depresores simultáneamente disminuye con la hipoventilación o después de inyecciones de cianuro para dar lugar a una sumación muy marcada.

Dentro de las condiciones experimentales en que se realizaron estas observaciones, la hipoxia e hiponventilación disminuyen (Fig. 4) o no modifican importantemente el efecto obtenido por la estimulación del cabo periférico del vago (Fig. 5).

Se concluye además que la secreción de adrenalina no ejerce un papel importante en la fenomenología descrita (Fig. 6).

Los autores agradecen al Dr. A. Rosenblueth las valiosas críticas y correcciones hechas al manuscrito.

Summary

Thirty experiments were performed in anesthetized rabbits (25 to 35 mg per kg, sodium pentobarbital). The depressor nerves were dissected in the cervical region. Cardiac frequency, electrical diaphragmatic activity and arterial blood pressure were recorded. The animals were kept under artificial respiration.

Hypoxia or hypoventilation enhances the reflex responses obtained by depressor stimulations (Fig. 1 and 2). This effect is independent of the lung volume, and mainly due to pulmonary chemoreceptor discharges that reach the cardioinhibitory centers.

When one vagus is cut, the response to ipsilateral depressor stimulation depends on the animal's ventilation. During hypoventilation or after cyanide, the responses become greatly enhanced. With bilateral vagotomy or atropinization the effect is abolished. The enhancement is thus due to an augmented vagal discharge.

The degree of temporal and spatial summation depends also upon ventilation. The frequency which the system follows, and the magnitude of the responses, are greater during hypoventilation or hypoxia than those found under hyperventilation or 100 per cent oxygen inhalation.

When simultaneous stimulation of the two depressor shows occlusion, this occlusion may change into important summation during hypoxia or hypoventilation or after cyanide injections.

Hypoxia and hypoventilation generally reduce or slightly increase the effect obtained by stimulation of the peripheral end of the cut vagi.

Adrenaline secretion does not play an important rôle upon these phenomena.

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PROCEEDINGS OF THE SOCIETY OF BIOLOGY
OF RIBEIRÃO PRETO (São Paulo, Brasil)

April 9, 1959

On possible central effects of bradykinin in the cat. A. P. CORRADO, A. O. RAMOS e M. ROCHA E SILVA. *(Department of Pharmacology, Faculty of Medicine, University of São Paulo, Ribeirão Prêto, State of São Paulo, Brazil).*

When injected intravenously in cats, bradykinin produces hypotension and estimulates respiration, by increasing the frequency and the amplitude of the respiratory movements. Destruction of the carotid sinus receptors and section of the vagus nerves diminishes but does not abolish the respiratory stimulus produced by bradykinin. Doses of bradykinin insufficient to produce visible effects when given by the intravenous route (3 units), still produce marked effects when given through the lingual artery into the carotid artery. The effect on the respiration (similar to that obtained by the injection of lobeline), is not abolished by destruction of the carotid sinus receptors, though the effect of the alcaloid, under strictly similar conditions is completely abolished by pinceling the carotid sinus region with a 10% solution of phenol. Also the fall in blood pressure following the intralingual injection of small doses of bradykinin persists after destruction of the carotid sinus receptors.

In cats, under anesthesia, bradykinin produces long lasting fall in arterial blood pressure when given into the cerebral ventricules (6 to 10 units). In the unanesthesized cat, bradykinin (15 units) was injected into the lateral cerebral ventricule, through a cannula according to the technique described by Feldberg and Sherwood, 1953. Symptoms of depression were observed in almost all animals injected with such doses of bradykinin. This ranged from slight sedation to complete apathy or strong tranquilization. In a certain percentage of animals, relaxation of the nictitating membrane could be observed. All the symptoms appeared immediately after the administration of the active material. In a certain percentage of animals, tonic convulsions occurred, concomitantly or not with a certain degree of sedation or depression. Only a small percentage of animals did not present symptoms after the administration of bradykinin into the cerebral ventricule. The respiratory effect was also evident in the unanesthesized animals given bradykinin through the ventricular cannula. Incubation of bradykinin with chymotrypsin abolished the symptoms induced by the intralingual administration of bradykinin.

Influence of sympatholytic agents and of reserpine on the hypotensive effect produced by bradykinin in cats. M. ROCHA E SILVA, A. P. CORRADO and A. O. RAMOS. *(Department of Pharmacology, Faculty of Medicine, University of São Paulo, Ribeirão Prêto, State of São Paulo, Brazil).*

Bradykinin, when injected intravenously in cats, rabbits and dogs, produces a sharp fall in blood pressure followed by a quick recovery and a subsequent secondary fall which may last a few minutes. This three phasic effect might be due to a release of catechol amines to explain the rise preceeding the secondary fall. This possibility was submitted to a test by using ganglioplegic (hexamethonium), sympatholytic (dibenzyline, chlorpromazine agents and centrally acting hypotensive drugs, such as reserpine and aprezoline. With the exception of the ganglioplegic drug utilized (hexamethonium) the other sympatholytic and hypotensive drugs strongly potentiated the effect of bradykinin on the cat's blood pressure. With moderate doses of bradykinin (10 to 30 units) injected i. v., a complete recovery to the original level can be observed after a short interval, of one or two minutes. However, when the animal has been treated with dibenzyline, chlorpromazine, aprezoline or reserpine, the same range of doses will produce a lasting fall for many minutes or hours. After a few alternating doses of bradykinin and of the sympatholytic agents (which *per se* will produce slight or no effect upon the blood pressure level), the arterial blood pressure tended to stabilize in the low level of 50 to 70 mm Hg. In consequence, a *mutual* potentiation mechanism has been postulated.

In order to further verify the idea that bradykinin might release catechol amines from peripheral stores, cocaine (10 mg per kilo, s. c.) was given half an hour prior to the injection of the test dose of bradykinin (60 units). In contrast with the sympatholytic agents, cocaine reduced the time for recovery from hypotension produced by bradykinin. Again, dibenzyline given afterwards and before a third injection of 60 units of bradykinin corrected the effect of cocaine and strongly potentiated the hypotensive effect of the new injection of bradykinin. The potentiation by reserpine might depend: a) of a depletion or significant reduction of the peripheral stores of catechol amines; and b) of a summation of the central effects of reserpine with those eventually produced by bradykinin, as described in the following communication.

Those results might bring forward the possibility that bradykinin, as an endogenous ubiquitary agent, might participate in the mechanism of the vaso-dilatation following the administration of sympatholytic agents and of reserpine. Other possibilities were discussed.

Exchanges in parabiotic rats studied in normal and nephrectomized animals. VICTORIO VALERI, SÉRGIO R. DOHI and JOÃO RODRIGUES DE SAMPAIO. *(Dept. of Histology. Faculty of Medicine. Ribeirão Prêto, São Paulo, Brazil).*

In the present investigation the exchanges in parabiotic rats were studied, estimating the blood urea, creatinine and serum ribonuclease activity, when one parabiont was nephrectomized bilaterally. Female adult rats were used. Animals of same size were surgically united by the open celomic method and were the most part litter mates. 20-30 days after parabiosis, a bilateral nephrectomy was performed in one parabiont. In this moment the first blood sample was collected, and others samples were taken at 48 and 72 hrs. after nephrectomy. In the control group the bilateral nephrectomy was performed in single animals and two blood samples were taken — at the time of operation and 48 hrs. after. The results are expressed in the following table:

	SINGLE RAT		ANIMALS IN PARABIOSIS			
	Before N.	After N. (48 hrs.)	Before nephrectomy	Hours after nephrectomy 48	Hours after nephrectomy 72	48 hrs. after sep. of the partner
Urea mg/100 ml	28.0 [37.1 / 21.1	466 [479 / 452	P.C. 26.0 [34.4 / 19.6 P.N. 31.5 [41.7 / 23.8	38.9 [51.5 / 29.4 128.9 [170.7 / 87.3	64.3 [85.2 / 49.7 149.6 [198.2 / 113.0	35.5 [47.0 / 26.8
Rnase act. (optical D x10³/10 1)	73 [112.2 / 33.8	192 [207.2 / 177.7	P.C. 148.6 [160.5 / 137.6 P.N. 134.5 [145.3 / 124.5		154.2 [166.5 / 142.8 236.3 [255.2 / 218.8	
Creatinine unities (optical D x10³/ 1)	161 [180 / 142	1269 [1274 / 1244	P.C. 110.0 [126.8 / 93.2 P.N. 103.0 [141.0 / 65.0		87.0 [101.9 / 72.1 317.0 [353.2 / 280.8	

N. - nephrectomy.
P. C. - parabiont control.
P. N. - parabiont nephrectomized (six pairs).
The values expressed are the mean and confidence interval.

These results demonstrate that the levels of the three substances are not the same in both rats. The normal levels of creatinine and Rnase activity were observed in the parabiont with kidney, but the urea was higher in both partners in about 72 hrs after nephrectomy. The normal blood levels were attained 48 hrs after desligation of the partners. Two possibilities were discussed: 1) the urea transported by the blood stream from the parabiont bilaterally nephrectomized to the parabiont control are constantly in excessive amounts, and the clearance rate is at an inferior level to depurate this urea; 2) a significant increase in the ureogenesis of both animals. With a temporary deficient clearance rate of the kidney of the non-operated parabiont.

PROCEEDINGS OF THE ARGENTINE SOCIETY OF BIOLOGY

Buenos Aires, November 6, 1958

Toxic and hypoglycemiant action of Chlorpropamide. J. APELBAUM. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires, Argentina).*

1) Chlorpropamide is a sulfonylurea having an intense hypoglycemiant and toxic action in dogs and rats.

2) Chlorpropamide exerts no role on the pancreatectomized dog.

3) Adrenalectomized dogs and rats are markedly sensitive to the hypoglycemiant and toxic action of chlorpropamide (the same fact observed with other sulfonylureas).

4) In normal dogs, the hypoglycemiant action of chlorpropamide seems to be more prolonged than that of tolbutamide and the toxicity more intense.

5) An adrenalectomized dog died 1 ½ hours after administration of 100 mg/kg of chlorpropamide, while those animals receiving 200 mg/kg of other sulfonylureas died 2 and 4 hours after administration. Chlorpropamide had a much more intense hypoglycemiant action than tolbutamide, in the first hour.

6) A dog with incomplete removal of the adrenals, received 100 mg/kg and in the third hour entered in irreversible coma. Two dogs with incomplete removal of the adrenals which were given 200 mg/kg of 2259 RP recovered and survived.

7) It is possible that mortality in dogs were due mainly to hypoglycemia.

8) In the white rat, the LD 50 is of 0,7 g/kg and for the tolbutamide 4 g/kg.

9) Glucose, hydrocortisone and adrenaline (as observed with other sulfonylureas) have protective effect in normal white rats.

10) Death in rats is mainly due to hypoglycemia.

11) Chlorpropamide is much more toxic than the other sulfonylureas.

Water absorption by the toad's skin. J. V. URANGA. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) The injection of vasopressin or toad's *pars neuralis* or dehydration enhance the uptake of water by the toad's skin. This fact takes place specially during the first hour, the duration of the response being prolonged in accordance with the increase of the stimulus.

2) The enhancement of water uptake produced by vasopressin and the toad's neurointermediate lobe, can be represented by the regression coefficient of the water uptake on the logarithms of the dose.

3) The regression coefficient of vasopressin and toads neurointermediate lobe are not significantly different.

4) The toad's neurointermediate lobe seems to be more active on the water uptake by the toad's skin, than on rats urine flow.

5) Small quantities of ClNa enhance the effect of the ox's posterior lobe of hypophysis.

6) Oxytocin is less active than vasopressin on tha toad's skin.

7) Dehydration provokes a marked increase on the water uptake by the skin in dead or living toads. This increase is similar to that produced by the injection of 1.000 U of vasopressin, equivalent to the content of 2.000 neurohypophysis. Water uptake becomes normal after four hours when the animals have recovered their initial weight, both in the dead and in the living toads.

8) Water uptake by the skin of dead or living toads is directly proportional to the loss of weight suffered by the animals.

9) The loss of water by the toad's skin increases with the osmotic pressure of a sucrose solution in which they are immerged.

10) Water uptake is higher in summer than in winter, but the sensitivity to vasopressin does not seem to change.

11) Total hypophysectomy or adenohypophysectomy produces an increase in the water uptake by the toad's skin.

12) The atrophy of the toad's neurohypophysis does not seem to enhance the water uptake.

Comparison between bradykinin and substance V. J. C. FASCIOLO, K. HALVORSEN, E. ZANGHERI y F. O. FERNÁNDEZ. *(Departamento de Fisiología. Facultad de Ciencias Médicas. Universidad Nacional de Cuyo, Mendoza, Argentina).*

Substance V is thermostable, resisting boiling during 20 minutes in HCl 0.1 N, but it is destroyed in its greater part under a similar treatment in Na OH 0.1 N.

It is dialyzable through cellophane membranes, resisting pepsin action, but is rapidly destroyed by chymotrypsin. It is also destroyed by crystallized trypsin, though it cannot be excluded that trypsin could be contaminated with small quantities of chymotrypsin.

It is rapidly destroyed by plasma, the latter loosing this property if previously incubated at pH 4 during 30 minutes at 37° C.

In these experiments, bradykinin and substance V showed similar behaviours, thus not excluding the identity of both substances.

Seminal vesicles and ovaries in hemidecorticated mice. R. H. MIGLIORINI and M. R. COVIÁN. *(Departamento de Fisiología, Facultad de Medicina, Ribeirão Prêto, São Paulo, Brazil).*

The effect of hemidecortication on the weight of seminal vesicles and ovaries of the mice is studied.

It is observed that both organs are larger in the operated animals, the difference being statistically significant.

The hypothesis is advanced that hemidecortication releases the hypophysis from some restrain action, either cortical or subcortical exerted through the hypothalamus thus resulting in an increased secretion of gonadotrophins.

Action of D.D.D. on the content of adrenal ascorbic acid in different animal species. V. G. FOGLIA, H. N. TORRES, J. A. MOGUILEVSKY and E. ASHKAR. *(Instituto de Fisiología, Facultad de Ciencias Médicas de Buenos Aires e Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

Ascorbic acid concentration has been measured in the adrenal glands of several species, after oral administration of D.D.D.

Dosis given to rats, dogs and frogs have been 0,5, 0,2, and 2 g/K/day respectively.

Sensitivity to action of the drug decreased in the following order: dogs, rats and frogs.

Ascorbic acid content in the adrenal gland was decreased after the 10th day of treatment in rats, the 6th day in dogs; frogs did not show any change.

On histological examination of the adrenal gland, atrophy was observed in dogs, congestion in rats and no change in frogs.

Body weight increase in toads injected with vasopressin or toad's neurointermediate lobe. J. V. URANGA. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) Vasopressin and neurointermediate lobe of the toad's hypophysis show the same activity on the weight increase of the toad.

2) The toad's body weight increase occurred when the animals are placed into water, is due to an increase in the water uptake by the skin, while the urinary flow keeps low.

3) The body weight increase produced by the neurohypophyseal hormones is due, mainly, to an inhibition of the urinary flow.

Inhibition of the spermiating effect of chorionic gonadotrophin. J. V. IRIARTE and M. H. BURGOS. *(Instituto de Histología y Embriología, Facultad de Ciencias Médicas, Universidad de Cuyo, Mendoza).*

The results obtained with two mucolytic inhibitors upon the spermatozoa release produced by 50 IU chorionic gonadotropin in toads are described.

The phosphorilated hesperidin (20 mg) does not inhibit the spermatozoa release.

Suramin, at same doses, produces a prolonged inhibition upon spermatozoa release.

An enzymatic mechanism in the spermiation is postulated.

Inactivation of oestrogenic hormone and experimental tumorigenesis of the ovary. E. FELS. *(Instituto de Maternidad "Prof. A. Peralta Ramos", Buenos Aires).*

In the ovary with ligature of its vascular pedicle, placed outside of the abdominal cavity between skin and muscle, the same tumor development takes place in almost the same percentage as in the ligated ovary, left inside the abdominal cavity. This fact is another proof that for the tumorigenesis the hepatic inactivation of the oestrogen hormone has not the importance which is generally attributed to this phenomenon.

Buenos Aires, November 20, 1958

Effect of calcium meso-oxalate on meta alloxan diabetes of rabbits. E. T. SEGURA. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) Calcium meso-oxalate showed a significant hypoglycemiant effect in the rabbit with meta-alloxan diabetes.

2) In the same experimental syndrome, calcium meso-oxalate reduced markedly the height of the glucose tolerance curve and decreased its peak.

3) Prolonged administration of calcium meso-oxalate produced permanent regression of diabetes in 30 % of the treated alloxan rabbits, prolonging significantly, in addition, survival with regard to the controls.

4) Calcium meso-oxalate provoked death in 50 % of the treated rabbits (5 out of 10 animals), causing gastric perforations probably due to local effect.

Changes produced by insulin on the effect of cortisone in the rat. J. C. PENHOS *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

Female rats weighing 85 to 95 g were treated with cortisone acetate (1 to 3 mg/rat/day) and insulin (4 to 10 U/rat/day) given subcutaneously during 10 days.

Insulin counteracted, partially or totally, the inhibitory effects of cortisone on growth, thymus, adrenals, uterus and frequency in the apparition of oestrus.

Influence of neurohypophyseal hormones and of hypophysis removal on the diuresis of the toad. J. V. URANGA. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) The neurointermediate lobe of toad's hypophysis has a similar activity on the toad's and on the rat's kidney.

2) Vasopressin is more active than oxytocin on the toad's diminution of diuresis.

3) The urinary flow has a seasonal variation but the sensitivity to vasopressin is the same in summer and in winter.

4) Removal of the hypophysis or removal of the *pars distalis*, or the section of the preoptic hypophyseal does not increase the toad's diuresis in winter. In a 40 % sucrose medium the urinary flow decreases in the same proportion in all the groups of operated animals.

5) Dehydration, either deep or slight, diminishes the urinary flow and in both cases it takes three or four hours before this urinary flow returns to normal, when the toads are placed back in water.

Curative action of yodothyroidectomy on the diabetes of the rat. N. ALTIERI, P. BAZERQUE and A. DENTI. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires y Comisión Nacional de Energía Atómica, Buenos Aires).*

It was studied the influence of yodothyroidectomy of white castrated male diabetic rats by subtotal pancreatectomy; the results were as follows:

The yodothyroidectomy had a curative action in a large percentage (75 %) of white rats, confronted with the control diabetic rats that were not treated with I^{131}.

Origin and development of germinal epithelium and Sertoli cells in the human testicle. Cytological, cytochemical and quantitative study. R. E. MANCINI, R. NARBAITZ and J. C. LAVIERI. *(Instituto de Anatomía General y Embriología, Facultad de Ciencias Médicas, Universidad de Buenos Aires).*

A histological, histochemical and quantitative study was made on sixty five normal human testes of different ages obtained through biopsy or necropsy. It included fetal, lactation, infantile, puberal and adult material. A histogram was used for studying quantitative variations

of the cell population of the seminiferous tubules and its significance was controlled by statistical methods.

It was observed:

1) There are two different kinds of cells in fetal seminiferous tubules: one is the primitive spermatogonium and the other the indifferent or sustentacular cell.

2) Both kinds of cells differentiate during childhood into divergent cell types, which at puberty give rise to the germinal line and Sertoli cells respectively.

3) The spermatogonial cells develop three waves of differentiation. The first two, which occur during fetal and infantile ages, respectively, are abortive. The third one, which starts during the second phase of puberty is continued effectively, and gives rise to the definitive spermatogenesis.

4) The Sertoli line presents a precursor type in the fetus, child and the first phase of puberty. An immature type appears during the second phase of puberty and a mature type after that.

5) The histochemical techniques showed that only the spermatogonial line has glycogen, lipids and nucleoproteins in all ages. Alkaline phosphatase was present during fetal age, disappeared at birth and reappeared in the second phase of puberty. The Sertoli line showed glycogen and lipids only in this latter age.

6) Statistical analysis of the applied histogram demonstrated significant variations in tubular diameter, total cell population, different types of spermatogonia and Sertoli cells in close relation with the already explained waves of differentiation.

7) The changes observed seem to correlate with given hormonal variations present in the fetus, child and puberal boy.

Effects of repeated insulin coma on the testicle of the rat. R. E. MANCINI, J. C. PENHOS, I. IZQUIERDO and J. J. HEINRICH. *(Instituto de Anatomía General y Embriología, Facultad de Ciencias Médicas, Buenos Aires e Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

A histological and histochemical study of the effects of one to five insulin coma on the testes of adult rats was made. Variable periods of recuperation after each coma by the administration of glucose were also studied.

Following observations were made: 1) Sloughing of the germinal epithelium, intercellular, cystoplasmic and nuclear vacuolization, picnosis and multinucleated germinal cells. 2) No nucleoproteins, glycogen or mucopolysaccharides were histochemically demonstrable in the vacuoles. These results are in accordance with our previous work. 3) The injuries increased in number and importance when comas were repeated. 4) Regression of the lesions was not complete even thirty four days after the coma. 5) The approximate distribution of the lesions in the cycle of the germinal epithelium was analysed. 6) The mentioned cytologic alterations seemed not to interfere with the dynamics of spermatogenesis; only one animal showed inhibition of the germinal epithelium.

Influence of the thyroid on the action of alloxan in the rat. N. ALTIERI, P. BAZERQUE and A. DENTI. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires y Comisión Nacional de Energía Atómica, Buenos Aires).*

The iodothyroidectomy decreases in the female white rat the sensitiveness to the toxic and diabetogenic action of alloxan.

The administration of thyroid powder (20 mg/100 mg/day) produces an increase of the sensitiveness to the toxic and diabetogenic action of alloxan.

Buenos Aires, April 2nd, 1959

Influence of the cerebral cortex on the sexual cycle of the albino rat. J. ANTUNES RODRIGUES. *(Departamento de Fisiología, Faculdade de Medicina, Ribeirão Prêto, São Paulo, Brazil).*

1) Hemidecorticate female rats show changes in sexual cycles. The periods between oestrus are lengthened and they remain in metaestrus in the intervals.

2) The archicortex in the part of the cerebral cortex responsible for this change.

3) The presence of many corpora lutea in ovaries and the prolonged metaestrus observed are indication of a greater secretion of progesterone.

Electron microscopy of the pancreas in rats treated with glucagon. P. E. LACY, A. F. CARDEZA, W. D. WILSON. *(Department of Pathology, Washington University, St. Louis, Mo.).*

The electron and light microscopic study of pancreas of force-fed rats receiving large amounts of glucagon was carried out. Moderate degranulation of beta cells was observed after three days of treatment, and also a wide dilatation of intercellular and pericapillary spaces of islets with development of long cytoplasmic processes of beta cells protruding into these spaces. At five and seven days after the treatment the spaces decreased in size returning to normal. Degranulation of beta cells increased progressively until the seventh day. There was not observed degenerative changes on the ultrastructure of the degranulated beta cells. The acinar cells were severe degranulated after one day of treatment and later numerous lipid droplets were present in their cytoplasm. There were no changes on the ultrastructure of alpha cells during all the period of observation. The animals presented severe hyperglycemia, glycosuria and weight loss. When the treatment was stopped during three days the blood sugar returned to normal and glycosuria disappeared; at the same time the changes of beta cells and acinar cells were reversible.

Interaction of levo-thyroxine and folic acid or aminopterin in the rat. J. C. PENHOS. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

The loss of body weight produced by levo-thyroxin in prepuberal female rats was not modified by folic acid or aminopterin. The atrophy of thyroid provoked by thyroxin was partially diminished by folic acid. The diminution of weight of thymus and uterus and of oestrus frequency were totally counteracted by folic acid. The adrenal increase of weight produced by aminopterin was not modified by levo-thyroxin.

Buenos Aires, May 7th, 1959

Autoradiographic study of I^{131} uptake by the thyroid in the toad. R. L. YÁÑEZ and M. H. BURGOS. *(Instituto de Histología y Embriología, Facultad de Ciencias Médicas, Universidad de Cuyo, Mendoza).*

This paper reports the results of the uptake of I^{131} by the thyroid of the normal, pituitary treated and hypophysectomized toads as studied by the radioautographic method.

Normal and pituitary treated animals show a very intense uptake of I^{131} in the colloid and a very poor one at the follicular epithelium level.

The number of radioactive follicles was higher in the pituitary treated than in the control.

By the other hand, the thyroid follicles of the hypophysectomized toad, show a very poor or negative uptake in the colloid and some uptake in the follicular epithelium.

Fixation of Fe 59 by the "ductuli efferentes" of the hamster. M. H. Burgos, H. Montes de Oca y N. M. Montorzi. *(Instituto de Histología y Embriología, Facultad de Ciencias Médicas, Universidad de Cuyo, Mendoza, Argentina).*

Adult hamsters were injected into the rete testis with radioactive iron citrate (Fe 59) and the ductuli efferentes were prepared according to the Pelc stripping film technique.

Most of the radioisotope activity was located in the epithelium of the ductuli, apparently concentrated in the cytoplasm of the non-ciliated cells.

A mechanism of absorption at the level of the nonciliated cells is postulated.

Associate effect of levo-thyroxine and insulin in the rat. J. C. Penhos and A. F. Cardeza. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

Female rats (85-95 g of body weight) were treated by L-thyroxin (20 μg/per rat, per day, per os) and/or insulin (2 U per rat, twice a day, subcutaneously), during 10 days.

Insulin counteracted totally or partially the diminution of body weight, uterus weight, and the frequency of oestrus.

Buenos Aires, June 4th, 1959

Action of different progestational steroids on the oviduct secretion of the toad "Bufo arenarum" Hensel. J. A. Blaquier. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) A stimulating action on the secretion of the glands of the oviduct of the toad *Bufo arenarum* Hensel was produced by many steroids.

2) 17α-ethynyl-19-nor-testosterone was the most active. By local route: it was twice as active as progesterone: Subcutaneously: 7 times as active as progesterone; per os: 8 times as active as progesterone.

3) Progesterone, the progestational type substance, lost $\frac{2}{3}$ of its action when given by subcutaneous and oral route, comparing with the injection in the oviduct lumen.

4) Adrenalectomy diminished 2.5 times the effect of 17α-ethynyl-19-nor-testosterone, while castration and hypophysectomy caused only a slight diminution.

5) Hydrocortisone inhibited the action of 17α-ethynyl-19-nor-testosterone while ACTH reinforced it.

Intrasplenic ovary graft in rats with ligature of the testicular pedicle. E. FELS. *(Instituto de Maternidad "Ramón Sardá", Buenos Aires).*

The development of an ovarian graft in the spleen of a rat with ligated testicular pedicles is possible only when the ligature produces complete destruction of the testicles.

The graft cannot develop when —as a consequence of the ligature— luteinized nodules of interstitial tissue appear in the testicle.

This fact is further proof that the newly formed interstitial tissue produces sex hormone which must be estrogen because the atrophy of the male genital tract excludes the presence of androgens.

Resistance to cold of adrenalectomized rats. C. M. GARRIDO. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

Survival to cold is shorter in the youngest rats and increases with age, during the first three months. Survival to cold is diminished in adrenalectomized rats (to about 40 % of the controls), but returns to normal after 60 days, due to the development of accesory adrenal. Unilateral adrenalectomy diminishes survival only slightly (15-25 %), but the resistance to cold is normal after 60 days. Demedullation of the adrenals diminishes survival time to cold (50 % of controls), but it progressively returns to normal after 90 days.

Córdoba, June 11th, 1959

Detoxification of urine by dialysis in the determination of chorionic gonadotrophins. J. J. ASTRADA, L. S. C. DE CALIGARIS. *(Instituto de Investigación Médica "Mercedes y Martín Ferreyra", Casilla de Correo 389, Córdoba).*

The advantages obtained on dializing urine directly when investigating chorionic gonadotrophins using male toads were studied:

1) Dialized urines were considerably less toxic than those not treated and conserved their gonadotrophic potencies.

2) 2 hours dialysis was sufficiently effective.

3) Common national cellophane paper was found to be as effective as imported cellophane tubes especially designed for dialysis.

4) If this procedure were incorporated in techniques for biological pregnancy reactions it would give low levels of hormone concentration wich is not shown with the common techniques.

Buenos Aires, July 2nd, 1959

Comparative study of the adrenolytic action between total extract of "Rauwolfia serpentina" and "Rauwolfia schueli". E. O. ZANGHERI, A. BINIA, J. C. FASCIOLO, J. I. CHIONETTI. *(Departamento de Fisiología, Facultad de Ciencias Médicas, Universidad de Cuyo, Mendoza).*

The adrenolytic action of an extract from the roots of *Rauwolfia serpentina* was compared

with two extracts of roots from *Rauwolfia schueli*; one of them was prepared from rootlets of big trees while the other from the cortex of thick roots.

These three extracts were found to have an adrenolytic action, but the one corresponding to *Rauwolfia serpentina* was, in all the doses essayed, about 20-40 % more active than the corresponding to the cortex of the big roots of *Rauwolfia schueli*.

No comparison could be made between the extract of the small roots of *Rauwolfia schueli* and the others, because of the lack of parallelism in the semilogarithmic curve relating dosis, to the reduction of the pressor effect of adrenaline.

Action of cortisone and sexual hormones in the rat. J. C. PENHOS. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

Female rat weighing 85 to 95 g were treated with cortisone acetate (1 mg/rat/day) and/or testosterone propionate (250 μg/rat/day) given subcutaneously during 10 days.

Estradiol benzoate given associated with cortisone acetate, modified the action of this hormone, as it intensified the fall of body weight and thymus involution; it counteracted the inhibitory effects on the uterus weight and on the frequency of apparition of oestrus, but did not modify fall of adrenals weight.

Progesterone increased the inhibitory effect of cortisone on body weight and on the frequency in the apparition of oestrus, but counteracted its characteristic action on the adrenals weight.

Testosterone counteracted partially the body weight fall produced by cortisone, and reinforced its inhibitory effect on thymus, adrenals and uterus weight and on the frequency of apparition of oestrus.

Indirect method for renin measurement in the Kidney. F. E. ALONSO, M. M. PUEBLA, J. C. FASCIOLO. *(Departamento de Fisiología, Facultad de Ciencias Médicas, Universidad de Cuyo, Mendoza, Argentina).*

An indirect method for the estimation of the renin content of the Kidney is described. It is based on the amount of angiotensin produced "in vitro" by incubating a renal extract free of angiotensinase with an excess of angiotensinogen. The angiotensin formed is estimated by its pressor action on the anesthetized rat.

The effect of acidifying the renal extract on the angiotensinase content has been investigated. It was found that, under our experimental conditions all the angiotensinase is destroyed, while preserving the renin content of the extract.

The estimation can be carried out using only a few milligrams of fresh renal tissue and amounts of renin of the order of 0.01-0.001 Units of renin (dog Units) can be detected.

Action of different substances on the resistance to cold in normal and adrenalectomized albino rats. C. M. GARRIDO. *(Instituto de Biología y Medicina Experimental, Obligado 2490, Buenos Aires).*

1) The time of death due to intense action of cold in adrenalectomized rats operated 7 days before, was not modified by glucose administration (20 mg), ascorbic acid (70 mg), ACTH (5 mg), STH (1 mg), levo-thyroxine (6 γ), adrenaline (20 γ), DOCA (3 mg) and 19-nor-methyl-testosterone (3 mg).

2) Normal rats were not protected by the administration of glucose (20 mg) or STH (1 mg).

3) The time of survival in albino rats under the effect of intense cold, was prolonged by the administration of cortisone (1 mg), cortisol (0.3 mg), prednisone (0.2 mg), 2-methyl-9-

chlor-hydrocortisone (0.2 mg) and dexamethasone (0.02 mg). Progesterone had a less protective action.

4) Increased resistance was observed in normal rats treated seven days before with ACTH (5 mg), prednisone (0.2 mg) and ascorbic acid (70 mg).

5) The resistance of adrenalectomized rats operated 60 days before (with accessory adrenals) was not increased by the injection of adrenocorticotrophin (5 mg).

Effect of oestradiol on the male rat. Influence of way of administration. J. A. MOGUILEVSKY, A. GUTIÉRREZ, M. R. MALINOW. *(Instituto de Fisiología, Facultad de Ciencias Médicas, Universidad de Buenos Aires).*

Weekly administration of estradiol microcrystals in male rats proved to have less effect on body weight and on the weight of several endocrine glands, that the same hormone when given parenterally in oil solution. Intravenous microcrystal have less action than intramuscular microcrystals.

Mechanism of the pressor effect of the spider "Latrodectus mactans" venom. II) Study with Starling cardiopulmonary preparation. R. CALVO, I. J. CHIONETTI, J. C. FASCIOLO, E. O. ZANGHERI, A. BINIA. *(Departamento de Fisiología, Facultad de Ciencias Médicas, Universidad Nac. de Cuyo, Mendoza, Argentina).*

The venom of the spider *Latrodectus mactans* was assayed in the isolated dog's heart, using a Starling heart-lung preparation. No changes in the heart output, were observed in the ten experiments performed.

Compañía Impresora Argentina S. A.
Alsina 2049 – Buenos Aires

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Las citas bibliográficas se harán en el texto mediante números [por ej.: algunos autores [2, 18] y en especial Jones [5]] o autores y año [por ej.: (Breslauer, 1919)]. Al final del trabajo la bibliografía se ordenará alfabéticamente y con numeración progresiva, en el primer supuesto, y alfabéticamente en el segundo. Para las abreviaturas de las revistas, etc., se seguirán las recomendaciones del World List of Scientific Periodicals. La disposición de tales citas debe ajustarse a los ejemplos siguientes:

(1) Houssay, B. A., Lewis, J. T., Orías, O., Braun Menéndez, E., Hug, E., Foglia, V. G., Leloir, L. F.: *Fisiología Humana*, 3ª edición, El Ateneo, Buenos Aires 1954.

(2) Whittembury, G., Ramírez, M., Fernández, J., Monge, C.: *Acta physiol. latinoamer.*, 1955, *5*, 117.

De acuerdo con el carácter del artículo (artículo de conjunto o comunicación original) constará o no el título completo de los trabajos citados en la bibliografía.

Las medidas y símbolos deben expresarse de acuerdo con las recomendaciones de la Comisión de Símbolos, Unidades y Nomenclatura de la Unión Internacional de Física, aprobados en Amsterdam, en junio de 1948 (*Cienc. e Invest.*, 1949, *5*, 433).

SE EXPONEN A CONTINUACION ALGUNAS ABREVIATURAS COMUNES

	Castellano	*Inglés*		*Castellano*	*Inglés*
metro	m	m	milisegundo	ms	msec
centímetro	cm	cm	litro	l	l
milímetro	mm	mm	centímetro cúbico	cm^3	cc
micrón	μ	μ	mililitro	ml	ml
milimicrón	$m\mu$	$m\mu$	kilogramo	kg	kg
Angström	Å	Å	gramo	g	gm
microgramo	μg	μg	miligramo	mg	mg
gama	γ	γ	miliequivalente	mEq	mEq
hora	h	hr	Curie	c	c
minuto	m	Min	Milicurie	mc	mc
segundo	s	sec	Microcurie	μC	μC
			por ciento	%	%

Para evitar la confusión derivada de la notación decimal diferente según los países, se adopta el punto decimal y se suprime toda notación entre millares sustituyéndose por un espacio: 10 000 (no 10.000 ni 10,000) —0.90 (no 0,90).

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SUMARIO